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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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MOLECULAR AND CLINICAL GENETICS PANEL

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March 27, 2014
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

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STEVEN SKATES, Ph.D.	Temporary Voting Member
JO-ELLEN DeLUCA	Patient Representative
DAVID W. GATES, Ph.D.	Industry Representative
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M E E T I N G

(8:00 a.m.)

DR. PRZYGODZKI: I'd like to call the meeting of the Molecular and Clinical Genetics Panel of the Medical Device Advisory Committee to order.

I'm Ron Przygodzki. I'm the Chair of the Panel. What I do, I am an anatomic and clinical and molecular genetics pathologist. I work for the Department of Veterans Affairs in the Office of Research and Development. I oversee preclinical studies for the VA.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel Members participating in today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket approval application sponsored by Exact Sciences Corporation for Cologuard.

Before we begin, I would like to have our distinguished Panel Members and FDA staff seated at the table to introduce themselves. Please state your name and affiliation.

DR. GATES: David Gates, Senior Director, Regulatory Affairs, Roche Molecular Systems.

MS. DeLUCA: Jo-Ellen DeLuca, Patient Representative, Colon

Cancer Solutions.

MS. FURLONG: Pat Furlong, Consumer Representative, foundation leader for Duchenne Muscular Dystrophy.

DR. MAHOWALD: Mary Mahowald, University of Chicago, bioethics.

DR. WECK: Karen Weck, University of North Carolina.

DR. LIPKIN: Steven Lipkin, Weill Cornell College of Medicine, Department of Medicine, Genetic Medicine, and GI and Hepatology.

DR. BUJOLD: Ed Bujold, primary care physician in private practice, Granite Falls, North Carolina.

DR. HICKS: Terry Hicks, academic surgeon, Ochsner Clinic, New Orleans.

MS. WATERHOUSE: Jamie Waterhouse. I'm the Designated Federal Officer for FDA.

DR. CAGGANA: Michele Caggana, New York State Department of Health, newborn screening and molecular genetics.

DR. McSHANE: Lisa McShane, statistician, National Cancer Institute.

DR. SKATES: Steven Skates, Massachusetts General Hospital, biostatistician, Harvard Medical School.

DR. NOSTRANT: I'm Tim Nostrant, Division of Gastroenterology, University of Michigan.

DR. GALLAGHER: Colleen Gallagher, bioethicist, the University of Houston, MD Anderson Cancer Center, Houston.

DR. GUTIERREZ: Alberto Gutierrez. I'm the Office Director for the Office of In Vitro Diagnostics and Radiological Health at the FDA.

DR. PRZYGODZKI: Thank you, folks.

Members of the audience, if you have not already done so, please sign in at the desk, that's as you walk into the conference room.

Jamie Mae Waterhouse, who is the Designated Federal Officer or DFO for the Molecular and Clinical Genetics Panel, will make some introductory remarks for the group.

MS. WATERHOUSE: The Food and Drug Administration is convening today's meeting of the Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S. Code Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this

Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S. Code Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S. Code Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and vote on information related to the premarket approval application for the Cologuard device sponsored by Exact Sciences Corporation. Cologuard is an in vitro diagnostic device designed to analyze patients' stool for detection of hemoglobin, multiple DNA methylation and mutation markers, and the total amount of human DNA. Cologuard is intended for use as an adjunctive screening test for the detection of colorectal neoplasia-associated DNA markers for the presence of occult hemoglobin in human stool. A positive

result may indicate a presence of colorectal cancer or premalignant colorectal neoplasia. Cologuard is not intended as a replacement for colonoscopy. Cologuard is intended to be used in conjunction with colonoscopy and other test methods in accordance with recognized screening guidelines.

Based on the agenda for today's meeting and all financial interests reported by the Panel Members and consultants, no conflict of interest waivers have been issued in connection with 18 U.S. Code Section 208.

Dr. David Gates is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Roche Molecular Systems.

We would like to remind Panel Members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript.

Pursuant to the authority granted under the Medical Devices

Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27th, 1990, and as amended August 18th, 2006, I appoint the following individuals as voting members of the Molecular and Clinical Genetics Panel for the duration of this meeting on March 27th, 2014:

Dr. Lipkin, Dr. Caggana, Dr. Hicks, Dr. Bujold, Dr. McShane, Dr. Nostrant, and Dr. Skates.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This has been signed by Dr. Jeffrey Shuren, Director of the Center for Devices and Radiological Health, on March 19th, 2014.

For the duration of the Molecular and Clinical Genetics Panel meeting on March 27th, Ms. Jo-Ellen DeLuca has been appointed as a temporary non-voting patient representative. For the record, she serves as a consultant to the Gastrointestinal Drugs Advisory Committee in the Center for Drug Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting.

Before I turn the meeting back over, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting. Their telephone number is (410) 974-0947.

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

Handouts of today's presentations are available at the registration desk.

The press contact for today's meeting is Jennifer Haliski.

I would like to remind everyone that members of the public and press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you would like to present during today's Open Public Hearing session, please register at the front desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time.

DR. PRZYGODZKI: Thank you.

So now is when we move to the Sponsor's presentation.

I would like to note to the public that while this an open meeting, to refrain from commentary unless you absolutely have a burning desire and you come to me and let me know about that.

If the Sponsor is ready, you have 75 minutes.

MR. CONROY: Thank you, Chairman and Panel.

My name is Kevin Conroy. I am the chairman and CEO of Exact Sciences. We appreciate your time and attention today.

I would also like to thank the entire team at Exact Sciences that has devoted so much time and effort -- and our collaborators -- to the development of Cologuard. And a special thanks to the investigators at over 90 sites in the DeeP-C clinical trial. And also a special thanks to the over 10,000 patients who volunteered to enroll in the trial.

This morning you will hear from some of the leading experts on colorectal cancer screening. First, you'll hear from Dr. Bernard Levin, who will speak on the biological progression of the disease and the background regarding colon cancer screening. Dr. Levin has served on numerous colon cancer screening guideline committees and formerly was a gastroenterologist with the University of Texas MD Anderson Cancer Center, from which he retired as the vice president of cancer prevention.

Then Dr. David Ahlquist will talk about the rationale for stool DNA screening and the biological basis for stool DNA screening. Dr. Ahlquist is a gastroenterologist, professor of medicine, and researcher with the Mayo Clinic. He is also a co-inventor of Cologuard.

Then you'll hear from Dr. Graham Lidgard. Graham is Exact's chief science officer. He will delve into the test, how it works, and how it was developed. Dr. Lidgard led the team that developed Cologuard. Previously, he led the team that developed the world's first and leading molecular

diagnostics blood screening system for HIV, hepatitis B, and hepatitis C.

Next, Dr. Tom Imperiale, the principal investigator in our DeeP-C study, will present the pivotal study design and the results. Dr. Imperiale is a gastroenterologist and a colorectal cancer researcher with Indiana University.

Sandra Statz, Exact's vice president of clinical quality and regulatory affairs, oversaw the DeeP-C clinical trial and she will speak to the post-approval study.

Then Dr. Sidney Winawer will speak about colon cancer screening guidelines and where Cologuard might fit into the current standard of care. Dr. Winawer is a gastroenterologist at Memorial Sloan Kettering Cancer Center who has chaired several colon cancer screening guidelines committees.

These additional speakers will also be available to answer questions, including Dr. Itzkowitz, who is an inflammatory bowel disease specialist with Mount Sinai; Dr. Harvey Kowaloff, who is a primary care physician and VP of medical affairs; and Dr. Charlotte Owens, who is an OB/GYN with Morehouse School of Medicine. We also have two biostatisticians to answer questions.

Why are we here today? We're here to talk about a screening test that will address a very important need. We know that colon cancer is the number two cancer killer in the United States among men and women.

Last year it was diagnosed in 130,000 patients and caused 50,000 deaths in the United States. Despite being known as the most preventable cancer by many, last year it was a big, big problem in the U.S., and it's going to be a big problem again this year. Without further improvement in our screening tools, the sad reality is that 1 out of 17 of us in this room will be diagnosed with this terrible disease.

In 2009, when I joined Exact Sciences, three of my friends were diagnosed with colon cancer, one of whom died. We've all been touched by this disease.

We know, though, that screening for colon cancer works. It reduces both the incidence of the disease and the mortality of the disease. The problem is that one-third of patients are not completing recommended screening. Approximately 60% of patients diagnosed with the disease are diagnosed in Stage III or IV instead of maybe at Stage I and II when the disease is eminently curable. We can and we must do better.

Cologuard is a stool-based DNA test that relies on the principle that premalignant lesions and colorectal cancer shed cells with altered DNA that are detectable in a stool sample. Cologuard is a novel test that relies on the power of both DNA and hemoglobin in Exact's FIT test in a combined manner to generate a single screening test result.

As you will hear from other speakers, the results of the DeeP-C study met the pre-specified primary and secondary endpoints, the primary

endpoint being the sensitivity and specificity for cancer detection. It is important to note that Cologuard achieved 92% cancer detection and 94% cancer detection in Stage I and Stage II cancer patients, with an 87% specificity and a 90% specificity in patients with a clean colon, with no colonic findings. The sensitivity for the precursor lesions most likely to progress to cancer, the sensitivity there was 69%. And the negative predictive power of the test was 99.94% for ruling out colon cancer.

The secondary endpoint was a comparison to the FIT test. Cologuard demonstrated statistically significant superiority over the FIT test for both colon cancer and advanced adenoma sensitivity. As Dr. Tom Imperiale will talk about, Cologuard offered a nearly 20 percentage point improvement over the FIT test for both cancer and advanced adenoma.

We believe that the data show that the balance of the benefits and the risks strongly favors Cologuard, which is a meaningful improvement over the current noninvasive test, the FIT test.

The data we are presenting to you today represent the culmination of nearly 20 years of work, going back to 1995 with early research into DNA biomarkers associated with colon cancer. The culmination of this work represents the dedication of hundreds of people as well as a major advancement in product design and development.

The optimization studies that you will hear about from Dr. Lidgard began in 2010. These studies were rigorously conducted to

ensure optimal sensitivity and specificity across the screening population.

In 2009, Exact began discussions with the FDA. The company, in consultation with the professionals at the FDA, felt that it was paramount to demonstrate the efficacy and safety of this test in a massive trial that matched the population in which the test may someday be used.

In 2011, the FDA and the Medicare system, CMS, created a pilot program for parallel review, and Cologuard was accepted into the program, in which it would be evaluated by both agencies simultaneously. Both agencies provided input into the design of the DeeP-C study. We appreciate the leadership of both agencies in creating the program. If approved by the FDA and covered by CMS, this program would make it easier to allow the introduction of Cologuard to be accessed by both patients and physicians.

The DeeP-C study commenced enrollment in 2010 and completed enrollment in 2012. We submitted the data to the FDA in 2013.

These are the proposed indications for use. I'll highlight just a few key points. Cologuard is an adjunctive screening test that is intended to detect both colorectal cancer and premalignant colorectal neoplasia. The term "adjunctive" is meant to indicate that Cologuard, if approved, will be one of a menu of options for colorectal cancer screening, consistent with published guidelines. It is not intended as a replacement for diagnostic colonoscopy. It is intended for the average-risk population, not for patients who are at a higher risk for colorectal cancer.

We look forward to our discussion with the Panel as well as your input into the DeeP-C data for the Cologuard test. And we thank you for your time and your attention and your engagement today.

Now I will turn it over to Dr. Bernard Levin, who will provide an overview of colorectal cancer biology and screening.

Thank you.

DR. LEVIN: Mr. Chairman, members of the Panel, my name is Dr. Bernard Levin. As you've heard, I am a Professor Emeritus at the University of Texas MD Anderson Cancer Center. Mr. Conroy has provided some background as to my career. I am also proud to have been associated with some of the individuals in this room, on studies on the biological basis for development of occult blood studies and also molecular detection of colorectal cancer.

As disclosure, it's important to tell you that I'm being reimbursed for my time and travel today. I am also a scientific advisor to Exact Sciences, and I have been compensated for that work. I do not hold any equity interest in the company and have no financial interest in the outcome of this meeting.

It goes without saying that colorectal cancer is a major public health problem, and you are familiar with the devastating statistics. The biology of colorectal cancer favors screening, and specifically the precancerous lesions -- adenomas -- which progress slowly to cancer over

time. Screening is important in that it lowers incidence and mortality, and current noninvasive screening tests are beneficial, but the performance characteristics are suboptimal. A sensitive noninvasive screening option is needed that accurately detects both early stage cancers and important pre-cancers.

As a physician who has taken care of many patients with advanced colorectal cancer, I have always been struck by the beneficial effect that a successful screening strategy would have played in their lives and averted various serious outcomes.

The statistics for colorectal cancer are displayed here: 50,000 individuals who will die of colorectal cancer in the United States, and 137,000 new cases will occur this year.

We will be using some anatomical terms during the course of this presentation. And just to orient you, this is the right side of the colon and the left side of the colon. And what is important to glean from this slide is that neoplasms are increasing on the right side of the colon, both pre-cancers and cancers.

I have already alluded to the natural history of colorectal neoplasia, and I would like to elaborate on this. Depicted here, from normal colon to early adenomas, to intermediate adenomas, to late adenomas, to cancer, is the sequence of events that can occur in the colon. The development of adenomas into cancer is a slow process, perhaps lasting 10 to

15 years on average. And these lesions, as they increase in size, can exfoliate -- and you will be hearing more about that -- and can also bleed and eventually will develop into cancer.

Certain adenoma characteristics are worth underscoring. The size -- and they're measured in diameter, and we know that larger lesions are more likely to progress to cancer. The type as seen under the microscope: tubular, tubulovillous, villous, and most significantly, the sessile serrated version. And dysplasia, a cytological or cellular abnormality, can be classified into low grade and high grade, and the high-grade dysplasia lesions are the most likely to progress to cancer.

The term "advanced adenoma" will be used, and I want to define it: in terms of size, all adenomas ≥ 10 mm in diameter; the type where, under the microscope, the villous component comprises 25% or more of the adenoma; and dysplasia, high-grade dysplasia is present in these -- may be present in these advanced adenomas.

I want to place special emphasis on the critical importance of high-grade dysplasia in the pathway of development of colorectal cancer. High-grade dysplasia, found either in the conventional adenomas or in sessile serrated adenomas, is essentially carcinoma in situ and is on the pathway to the development of frank cancer.

The likelihood of an adenoma to contain high-grade dysplasia or itself become malignant is depicted here, and the association with size is

very clearly illustrated. The larger the lesion -- in this case 30 mm, 3 cm or greater -- is associated with almost a 50% presence of high-grade dysplasia.

Well, what are the lesions for which we want to be screening? They include curable stage cancer, advanced pre-cancers -- and these include large adenomas ≥ 2 cm -- large sessile serrated adenomas, and lesions that contain high-grade dysplasia.

It is worth making special mention of sessile serrated adenomas, a recently identified colorectal cancer pathway. These are associated with about one-third of colorectal cancers. They're hard to see. This arrow illustrates a lesion. And they don't bleed; they don't have the vascular markings that I illustrated in the earlier adenoma sequence. So these lesions are difficult to find for even the most skillful endoscopist.

Well, what is the rationale for colorectal cancer screening, and why is it suited for achieving its objectives? Firstly, the detection and removal of adenomas lowers incidence and mortality. Secondly, early detection and surgical resection of cancer lowers mortality.

Now, I want to illustrate the importance of the adenoma carcinoma pathway by two studies from the National Polyp Study, which was led by Dr. Sidney Winawer, from whom you will be hearing shortly. In the first study published in 1993, these investigators were able to show a 76% to 90% incidence decline in individuals in whom adenoma had been removed, compared to the general population and to reference groups.

In a subsequent study published in 2012 from the National Polyp Study, there was observed a 53% decline in mortality in those individuals who had had their adenomas removed, compared to the general population. Individuals in whom no adenomas were removed are illustrated here. These studies underscore the importance of removal of adenomas.

It is important to remind you of the relationship between stage of diagnosis and the outcome, the five-year survival rates of colorectal cancer. In the earlier stages, Stages I and II, which are surgically curable, the survival approximates 94% and 82%, respectively. When lymph node involvement has occurred, Stage III, or when distant metastasis has occurred, the outcomes are much less favorable. Even in spite of advances in therapy that have become established over the last few years, these still remain difficult to manage.

We have a menu of screening tests and their performance illustrated here, and they can be classified into invasive tests and the noninvasive tests. The invasive tests include colonoscopy, sigmoidoscopy, and CT colonography.

Their performance and respective sensitivities for colorectal cancer and advanced adenoma, as well as the specificity, are illustrated on this slide. And colonoscopy, approximately a 95% sensitivity for cancer and 95% for advanced adenomas and 90% specificity. Sigmoidoscopy, which examines the distal part of the colon, the left side predominantly, has about

half of that and with a high specificity. And CT colonography, which has similar performance to colonoscopy.

Of the noninvasive tests, fecal immunochemical testing has 70% sensitivity for colorectal cancer; 22% sensitivity for advanced adenomas with a high specificity of 95%. Guaiac fecal occult blood tests, the Hemoccult SENSA, a sensitive version of the guaiac tests, 70% sensitivity; but 24% for advanced adenomas, with 93% specificity. And the less sensitive older version of guaiac, Hemoccult II, 40% sensitivity for colorectal cancer, 12% for advanced adenomas with a 98% specificity.

The biological importance of adenomas and colorectal cancer as a basis for test performance is illustrated on this slide. As I've already shown you, the development of early-to-intermediate-to-late is a slowly progressive process, and although few adenomas become malignant, those that do are predominantly the larger lesions and those in which high-grade dysplasia is found.

Because of the slow progression, repeated screening over time has the potential to increase the detection rate, as contrasted with colorectal cancer, where Stages I to II are considered surgically curable, but the window of opportunity for detection of these lesions is narrower.

As you have already heard, the proportion of individuals in the United States who are unscreened is approximately one in three. So there may be 30 million individuals who are not receiving the benefit of colorectal

cancer screening at the present.

In summary, the desired characteristics of a new noninvasive sensitive colorectal cancer screening test are high sensitivity for early stage cancer, lesion detection throughout the colon, improved advanced adenoma detection, a balance of specificity with sensitivity, and safety and simplicity of use.

Thank you, Mr. Chairman and members of the Panel. I'd like to now to turn this over to Dr. David Ahlquist.

DR. AHLQUIST: Good morning. I'm Dave Ahlquist. I am a professor of medicine and a gastroenterologist at the Mayo Clinic.

As a disclosure, I am being reimbursed for my time and travel here today. I am also the inventor of the technology that has been licensed by Mayo Clinic to Exact Sciences. Under that agreement, I share equity and royalties. I was an investigator in the DeeP-C pivotal trial, and my institution was compensated for that work as well as for my time spent as a scientific advisor to the company.

So this concept of stool DNA testing has been around for a couple decades. Why has it taken so long to come to this point? In a simple word, technology. Exact Sciences has developed advanced technology that has allowed the biological and clinical promise of this approach.

In this very brief overview, I'll touch on the inherent limitations of fecal blood testing as a rationale to take noninvasive testing to a higher

level: the biological rationale for stool DNA and early development of the test.

A central issue with fecal blood testing is that neoplasms bleed inconsistently. This is a study we did more than 20 years ago, but it illustrates the problem. Hemoglobin in the stool is quantified for each of 10 patients with colon cancer who graciously provided stools, every stool for two weeks prior to their treatment. We expect a lot from patients.

And the blue line below there is the normal range, the 95% specificity range. As you can see, bleeding from colon cancer is intermittent. Some regions don't bleed at all. If you look at that patient, Number 5, endoscopically there's blood on the surface of the lesion, and hemorrhagic. Bleeding makes a lot of sense there. But in Patient 7, where a small cecal lesion that is not hemorrhagic -- fecal blood levels were never elevated. And if one showed the similar patterns for pre-cancers, bleeding levels are very low. The large majority of polyps do not bleed.

So how does this approach perform in the screen setting? Taking FIT, which has become the best and most accurate approach to detecting lower GI bleeding, the study by Morikawa is perhaps the most robustly done study. It was the largest and most completely evaluated. In that study, at 95% specificity, the sensitivity overall for cancer was 66%. Sensitivity was higher in advanced stage disease than lower stage disease. And for pre-cancers, the advanced adenomas, the sensitivity was quite low

even for high-grade dysplasia, only 33%.

Can we do better than this? Can we set the bar higher for noninvasive screening? And I think the answer is yes, as you will see in the presentations by Drs. Lidgard and Imperiale following this one. And why is that? Well, fecal DNA testing is fundamentally different -- fundamentally different. It is based on the biology of exfoliation.

Neoplasms develop localized changes, either genetic or epigenetic, and changes that are not present in the normal colon. Those changes persist in cells that are continuously exfoliated or shed from the surface of the neoplasm. Those cells break down and they're excreted along with cell debris. DNA fragments are recoverable, and those fragments retain the characteristic signatures of the presence of cancer or polyps and provide the basis of the DNA assay.

There is much evidence for exfoliation. It is abundant from cancer and adenomas; it is continuous in contrast to bleeding, which is intermittent; and it is much more luxuriant from cancer than from normal. These two images on your right, photomicrographs, demonstrate that. The colon is lined by a mucus layer, and when cells shed, they are temporarily entrapped in this mucus layer, and it provides a snapshot, pathologically, of exfoliation. It's much more abundant from cancer than normal, and we exploit that difference in this assay.

DNA was selected over time as the best marker class. We've

looked at RNA and proteins. They tend to be either up- or down-regulated but are not structurally different, where DNA is altered either by mutations or epigenetic changes. DNA is more stable and it can be amplified. So that aids in the detection of the analyte.

It's really important to understand that exfoliation occurs abundantly at all stages of cancer. It is independent of cancer stage. And it occurs equally abundantly from premalignant, pre-invasive, large adenomas, as shown here, the yellow arrows -- large arrows across all stages. In contrast, for markers to get into plasma, for example, blood vessels have to be invaded, and the degree of blood vascular invasion increases with stage of cancer. And abundant data in the literature show that marker levels in plasma increase in proportion to cancer stage. And tumor markers are not found in the plasma significantly at the pre-cancer level.

We and others have done direct comparisons between DNA in the stool and in the plasma and found that, in the stool, the sensitivity is much greater, especially for early stage cancers and pre-cancers. And fecal blood testing, on the luminal side, is also such that blood is in higher amounts with advanced cancer and the lowest amounts with the pre-cancers, in contrast to exfoliated markers.

So there were some challenges along the history of this approach. Finding the right markers was one, and with a variety of approaches, including whole genome sequencing, we've kind of settled on

the current panel of markers: two methylation markers and mutated KRAS at the tissue level. At the tissue level, they are 100% accurate. They, in 100% of cases, will detect cancer or pre-cancers, both types, and 100% of the time the normal mucosa are negative. So they are very discriminate, that combination, at the tissue level. And that combination has been taken most recently to stools and are now part of the Cologuard assay.

At the assay level and stool, there are challenges. The stool is full of inhibitors for PCR and other parts of the assay. Human DNA is a miniscule part of the overall DNA. Most of it is bacterial or dietary. Human DNA is a small fraction of 1%, and the tumor-related DNA is a fraction of that percent. So it's a needle-in-a-haystack challenge, and that's why the exquisitely sensitive analytical technology that's been developed is so critical to this approach.

So taking this new technology to recent case-control studies, the result has been very high sensitivity for cancer and the pre-cancers at highest risk. In the dark blue, there was a prototype assay that was applied to over 250 stools; and in the lighter blue, in a more optimized assay, to about 100 cancers. And the sensitivity of 98% was stunning. That's a range reported for colonoscopy, and it begs validation in a screen setting, which we'll report subsequently. And so the whole class of advanced adenomas, over 50%, and for the subsets that Dr. Levin mentioned, those with high-grade dysplasia, the sensitivity is substantially higher. That's the subset

where the outcome with respect to screening will have the greatest impact.

So my last slide here. I think we're witnessing a historical transition here from less sensitive fecal blood tests to a more sensitive noninvasive approach. The old approach of guaiac blood testing was limited by intermittent bleeding. That's why three tests per patient had to be done and the patients had to modify their diet and medications, because there were so many interfering factors.

FIT also measures hemoglobin, but the protein portion was an improvement, for sure. However, detection was still limited by the intermittency of bleeding. But, because it's more sensitive, a single sample is used and there are no dietary restrictions.

Stool DNA testing takes this whole approach of stool testing to a much higher level of sensitivity, and it's based on this continuous shedding -- a different mechanism -- of cells, a single assay, and no dietary or medication restrictions.

So that is a very brief glimpse of a background. I'm going to turn it over Graham Lidgard, who will go over the nuts and bolts of the assay.

Thank you.

DR. LIDGARD: Good morning. I'm Graham Lidgard, Chief Executive -- Chief Science Officer at Exact Sciences.

(Laughter.)

DR. LIDGARD: I've got aspirations.

I'm going to walk you through the assay and the development of the assay, the Cologuard algorithm, and the background of the assay. There's a very detailed description of the product in your package, and I'm willing to answer questions on those in question time, but I'm not going to go that deep into the details.

So the Cologuard system consists of three components, three elements: the sample collection kit; the sample analysis, where the assay is done in the lab; and then the results algorithm, which is calculated on the Exact system.

The collection kit is very simple to use. It's a home collection. The subject places the bracket and container under the stool container, provides a sample, removes the container, finishes their toiletry, and then takes a sample for hemoglobin. That sample goes into a tube with two metal buffers. It's a self-metering tube that controls the amount of stool that goes into the tube. And then once that's closed, the subject pours the stool stabilization buffer over the remaining stool, closes the container, packages the collection kit, and returns it to the clinical lab.

The sample analysis workflow. Once the sample arrives at the clinical lab, the two containers go into different paths. The hemoglobin sample goes through a semi-automated process. It's an ELISA-based hemoglobin assay, conventional ELISA plate, and the results are combined with the molecular at the end of the assay.

For the stool sample, the stool is diluted to a proportion of buffer to stool, mixed, centrifuged, and then the supernatant is taken through a capture procedure where the specific human DNA of the target that we're interested in is captured onto magnetic particles. And from that point on, the whole assay is automated.

It goes through DNA preparation. The DNA preparation is a bisulfate for half the DNA where we detect the methylation markers, and the other half of the DNA goes through a mutation analysis with -- both with the QuARTS assay. And we detect the seven mutations of codons 12 and 13 for KRAS in a single amplification mixture, and we detect the two methylation markers for QuARTS in a different amplification. So there are two amplification reactions on the same plate. The biomarkers are combined at the end in the algorithm to produce a single positive or negative result that's reported to the clinician.

The markers -- I'm not going to into detail, but the NDRG4 and BMP3 markers have been reported on. They're over-methylated, hypermethylated, in cancer, and they have an interesting biological pathway in cancer. The seven KRAS mutations are well known. They represent about 35% of all colorectal cancer tumors. And we use beta-actin DNA as a normalizer and a control sample in the DNA. If beta-actin is less than 200 strands, it's an invalid sample. So we measure the quality of the assay by the amount of DNA that's in the stool reaction. And, again, we measure the fecal

hemoglobin marker with our own FIT assay and combine those results.

So the biomarker results, they're all a quantitative assay. They all give a numeric value that's incorporated into the composite score. And if the score is ≥ 183, it's a positive. If it's < 183, it's a negative. And we only report the positive/negative to the clinician, as I described before.

For the development studies, we did three basic processes. The first was the optimization of the automated procedure. When we developed the assays, we ran over 2,000 samples, and we had over 250 colorectal cancers, 130 adenomas. And then once we fixed the assay in terms of determining its characteristics and its manufacturability, we went into the algorithm definition. And we used manufactured materials to define the algorithm. We used over 1,000 samples: 93 colorectal cancers, 114 adenomas. They were prospectively collected after diagnosis by colonoscopy, and they were used to define and optimize the algorithm. Once the algorithm was defined, it was fixed, it was programmed into the software, and we went into the DeeP-C study, which Dr. Imperiale will describe in more detail.

So the objective of the algorithm study was really to maximize the detection of both colorectal cancer and advanced adenoma. So advanced adenoma and colorectal cancer were the positive component. The normal non-advanced adenoma and colorectal cancer were the normal component. The subjects, as I said, went through colonoscopy; we measured all 11

markers, and the algorithm was built using a logistic regression model to define the logistic equation. And the cutoff was set at a nominal 90% specificity in that cutoff study.

The results of the cutoff study are shown here, where we have approximately equal detection across all stages of colorectal cancer. The sensitivity for advanced adenomas increases with size. And we have approximately equal detection across adenoma type, with a higher detection of high-grade dysplasia and significant detection of sessile serrated polyps. And sensitivity by location, there was no significant differences between proximal and distal for both adenoma and cancer.

I'm now going to describe the analytical testing methods. Again, they're detailed in your package. The key tests that I'm referring to, although all the values are reproducible, we only report the positive/negative results. So percent agreement between positive and negative is the endpoint of the reproducibility study, and we had 98% agreement between all laboratory tests at three sites, two operators at each site, 22 runs at each site, and the overall results showed that agreement for the manufacturing lots and for the laboratory sites. Overall, we had less than a 20% CV across all positive Cologuard scores.

Interference studies. The details of that, again, are in your package, in terms of all the materials we looked at. It was close to 50 substances that we tested for interference; foods, obviously animal DNA, and

anything that could be in the diet; pharmaceutical preparations that people take; and substances such as ointments and lotions that are used on the patients. And we also demonstrated stability over the time and shipment of the stool and the hemoglobin back to the lab, from the patient.

With that I'm going to turn it over to Dr. Imperiale to describe the results of the DeeP-C study.

Thank you.

DR. IMPERIALE: Good morning. I'm Tom Imperiale, Professor of Medicine at Indiana University, and I am a gastroenterologist and health services researcher.

In terms of disclosure, I was the lead investigator on the DeeP-C study. Indiana University was compensated for my effort on that study. They're being compensated for my effort here today as part of this presentation.

So I will now present the methods and results of the DeeP-C study. These results were published last week online in the *New England Journal of Medicine*. They will be available in the next issue, April 3rd.

The primary objective of the study was to determine the sensitivity and specificity of Cologuard for colorectal cancer. The secondary objective was to compare sensitivity and specificity of Cologuard to FIT for colorectal cancer and advanced adenomas.

This prospective, multicenter study required 90 sites to enroll

more than 10,000 subjects, all of whom were required to complete Cologuard, FIT, and colonoscopy. The protocol was designed with input from national experts in colon cancer screening, the FDA, and CMS.

Primary endpoints for the study, sensitivity and specificity, were discussed and agreed upon with the FDA. The lower 95% confidence limit, 65%, was based on the largest published study of FIT performance by Morikawa, that you heard about earlier, in which 65% was the point estimate for sensitivity. The goal was to have the lower 95% confidence limit for Cologuard be no lower than this point estimate. The low limit for specificity of 85%, which was chosen to maximize sensitivity while attaining a clinically acceptable threshold for specificity.

Secondary endpoints included a comparison between Cologuard and FIT on sensitivity for colorectal cancer, and this included being able to show both non-inferiority and superiority to FIT, as well as sensitivity comparison for advanced adenomas to show superiority of Cologuard.

Eligible for the study were adults ages 50 to 84 with average risk for colorectal cancer; that is, no history of colorectal cancer, adenomas, aerodigestive tract cancers, or high-risk conditions for colon cancer, such as inflammatory bowel disease; no family history of familial polyposis or non-polyposis colorectal cancer syndromes; no positive occult blood test within the previous six months; no colorectal cancer resection for any reason except sigmoid diverticular disease; and no overt rectal bleeding within the

past 30 days. And they had to be due for screening, which meant no colonoscopy within the previous nine years, no barium enema, sigmoidoscopy, or virtual colonoscopy within the previous five years.

The discussed endpoints and thresholds required inclusion of between 49 and 55 colorectal cancers to power the superiority of Cologuard over FIT. The number of cancer cases required to power the primary endpoint, that is, Cologuard sensitivity, was actually lower than for demonstrating superiority over FIT. With an expected cancer prevalence rate of 5 per 1,000, that resulted in an estimated participant sample size between 10,000 and 12,000.

Ninety sites were recruited nationwide and in Canada to assemble a representative study population.

Eligible subjects were consented and enrolled. They collected a stool sample at home, which was sent for testing to one of three laboratories. Subjects had colonoscopy within 90 days of enrollment. Histopathology was evaluated by local pathologists on any biopsies or excised lesions, with certain findings undergoing independent central review to confirm those findings. Cologuard and FIT test characteristics were based on colonoscopic findings as the reference or gold standard.

The findings were categorized as follows: Category 1 included all colorectal cancers. Category 2 included advanced adenomas. Subcategories were based on the subtype of advanced adenomas. And I'll say

more about these shortly. Categories 3 through 5 were used to classify non-advanced adenomas. These were considered negative findings. And Category 6 consisted of negative findings, which included non-neoplastic lesions, so things like hyperplastic polyps, lymphoid aggregates, and others; and so-called clean colons, that is, no lesions detected, no biopsies taken.

The next several slides describe the study population.

Nearly 12,800 persons were enrolled. Just over 10,000 were included in the primary analysis of Cologuard test characteristics, and just under 10,000 were included in the secondary analysis comparing sensitivity of Cologuard and FIT for colon cancer and advanced adenomas.

Among the nearly 2800 excluded subjects, 464 withdrew consent; 1,168 never underwent colonoscopy; 304 had an unusable colonoscopy; 128 did not provide a stool sample; 474 provided an unusable stool sample; and 213 had no Cologuard result.

The study sample was comprised of 54% women, 46% men, proportions that reflect the gender distribution of the U.S. population within that age range.

The study sample was nearly 84% Caucasian, 11% black or African American, and 5% other, reflecting the racial distribution of the U.S. population.

Ethnically, 90% of the subjects were non-Hispanic, again reflective of the U.S. population within that age range.

While mean age of the study population was comparable to the U.S. population, a difference of a year and a half, the distribution, seen here, reflects the strategy of age enrichment, which was used to ensure identifying an adequate number of colon cancer cases and having adequate representation of persons age 65 and older, as agreed upon with CMS and the FDA.

Among the 10,023 subjects included in the primary analysis, 65 had colorectal cancer, 760 had one or more advanced adenomas as the most advanced lesion, just over 2900 had non-advanced adenomas, and the rest, nearly 6300, had a negative colonoscopy. This includes both clean colons and non-neoplastic findings. Colorectal cancer prevalence ensured enough cases for the secondary analysis and was consistent with cancer prevalence found in a screening population of about five cancers per 1,000.

The next several screens show the study results, and these consist of the numerical results for the primary and secondary endpoints and statistical analysis of those endpoints, including ROC curves. I'll also report subgroup analyses based on demographics, colon cancer stage, location, and advanced adenoma type, size, and location.

Point sensitivity for Cologuard was 92.3%. It detected 60 of 65 cancers, with a two-sided confidence interval of 83% to 97.5%. The one-sided 95% lower bound is 84.5%, which exceeds the projected lower bound of 65%.

Point specificity was 86.6% with a 95% confidence interval of

85.9% to 87.2%. The one-sided lower confidence bound was 86%, exceeding the projected lower bound of 85%.

Sensitivity of Cologuard -- seen in the blue bar, 92.3% -- was nearly 20% higher than that of FIT -- in red, 73.8%. And this difference was statistically significant. FIT specificity was 94%. A comparison between specificities was not a statistical endpoint for the study.

Sensitivity of Cologuard for advanced adenoma was 42.4% as compared with 23.8% for FIT, and this difference was statistically significant.

This two-by-two table compares Cologuard and FIT for concordant and discordant results for detection of colon cancer. Thirteen cancers that were missed by FIT were detected by Cologuard, whereas just one cancer missed by Cologuard was detected by FIT. This difference was statistically significant.

This is a similar table for advanced adenoma, where Cologuard detected 170 advanced adenomas missed by FIT, whereas FIT detected 29 advanced adenomas missed by Cologuard. Again, the p-value for the difference was statistically significant.

This figure displays and compares the two tests for their colon cancer test characteristics. ROC curve areas were in the very good range for FIT, seen in the solid blue line, and in the excellent range for Cologuard, the broken red line.

In summary, Cologuard sensitivity for cancer, advanced

adenoma, and the combination exceeded that of FIT and in each case by an absolute difference approaching 20%.

Now I'll present subgroup analyses, first by demographics.

In subgroups of sex, race, ethnicity, and age category, the cancer sensitivity of Cologuard remained numerically greater than that of FIT, with absolute differences ranging from 11% to 30%.

Here are results of sensitivity of advanced adenoma by demographic subgroup. The difference between Cologuard and FIT was consistent across all subgroups except for the oldest age group, where there were just 15 advanced adenomas.

Here's the cancer specificity of Cologuard by demographic subgroup. Specificity was inversely related to age. It was highest in those participants younger than age 60 (92.2%); lowest in those age 75 and older (78%). Specificity did not vary with sex or race or ethnicity.

Here's a comparison of Cologuard and FIT for the cancer sensitivity based on cancer stage. Cologuard sensitivity, the blue bars, was greater than that of FIT, seen here in red, for Stage I and II cancers, the most curable stages.

Here is a comparison of the two tests for advanced adenoma sensitivity based on adenoma subgroup. Cologuard sensitivity numerically exceeded that of FIT for all subgroups. Results in two subgroups are worth noting in particular. One is that containing polyps of high-grade dysplasia for

which Cologuard sensitivity was 69.2% versus 46.2% for FIT. These lesions have the highest risk for short-term advancement to invasive cancer. The second subgroup are the large serrated lesions, which are frequently difficult to identify endoscopically and are believed to be the cancer precursor lesion for up to one-third of colorectal cancers and tend not to bleed, as supported by the 5.1% sensitivity for FIT in comparison with 42.4% for Cologuard.

Here is a comparison of Cologuard and FIT based on adenoma size. The sensitivity of both tests increased as adenoma size increased, with Cologuard, in blue, showing greater sensitivity in all size categories. Adenomas 20 mm or larger have a high risk of rapid progression to cancer.

In considering cancer location within the large intestine, Cologuard sensitivity was consistent, irrespective of location, and numerically greater than FIT in all three locations.

As compared to the proximal colon, advanced adenoma sensitivity was higher for both tests in the distal colon and rectum. Cologuard sensitivity exceeded FIT in all three locations.

In considering Cologuard specificity within the subcategories of negative, we see that specificity was lower when larger, seen in Category 3, or more numerous, in Category 4, non-advanced adenomas were present. And it was highest when colonoscopy was totally negative, meaning no lesions or polyps of any kind were identified (89.8%).

And within these categories, here's how the false positive

Cologuard test results break down. Forty percent of the false positives were in subjects who had non-advanced adenomas, reflecting some ability of the test to detect non-advanced neoplasia. Twenty-three percent of those occurred with non-neoplastic findings that were biopsied, and the remaining 37% were in subjects with clean colons.

In summary of the study's endpoints, Cologuard had a cancer sensitivity of 92.3%, a lower 95% confidence limit of 84.5% exceeding the 65% lower bound anticipated as the study design and sample size were established. Cologuard's cancer specificity of 86.6% has a lower 95% confidence limit of 86%, exceeding the 85% lower bound. Its cancer sensitivity was both non-inferior and superior to FIT. Cologuard sensitivity for advanced adenomas was superior to FIT by an absolute difference of nearly 20%.

To put these results in a clinical context, let's compare the numbers needed to treat, or the numbers in this case needed to screen for clinically important findings among colonoscopy, Cologuard, and FIT.

The number needed to screen is the number of persons that need to be tested to identify one person with a particular finding. In this case, we'll consider three findings: any colorectal cancer, Stage I to III cancer, and advanced pre-cancerous lesions. The number needed to screen is a measure that considers the test characteristics and the prevalence of the finding.

To identify one person with any colorectal cancer, the number needed to screen is 154 for colonoscopy. It's 166 for Cologuard and 208 for FIT. For Stage I to III cancers, you see that all numbers needed to screen increase slightly. For advanced adenoma, the numbers needed to screen are 13 for colonoscopy, 31 for Cologuard, and 55 for FIT. These numbers suggest that Cologuard detected clinically significant lesions more efficiently than FIT.

What about Cologuard safety? The risks include direct risks, that is, from doing the test itself, and the indirect risks, that is, the consequences of false positive and false negative results.

Cologuard has a very low direct risk. It is noninvasive, requires no bowel preparation or dietary restriction, and the collection kit allows the specimen to be collected during a normal bowel movement. In the DeeP-C study, no serious adverse events related to the stool collection process were reported, and there were four events, all of which were mild.

In considering the false positive risk, this table quantifies and compares findings and adverse events in a hypothetical cohort of 100,000 people who would be screened with colonoscopy, Cologuard, and FIT. Despite the numbers of false positive results for Cologuard and FIT -- and these are greater for Cologuard because of its lower specificity -- major adverse events are much lower for both noninvasive tests, as expected, and the ratio of serious adverse events per cancer and adenoma detected are nearly identical for Cologuard and FIT; and both are lower than with

colonoscopy.

False negative results could potentially delay detection of disease -- this is true as well for FIT -- with Cologuard having 71% fewer negative tests among those with cancer, 43% fewer negative tests among those with high-grade dysplasia, and 24% fewer among those with advanced adenomas.

Let's consider the study results that support Cologuard's benefit as a screening test. These include high sensitivity for early stage cancer, detection throughout the colon, ability to detect advanced adenomas, and an acceptable balance of specificity with sensitivity, as well as safety and simplicity. Let's each consider these now in turn more specifically.

Cologuard has high sensitivity for cancer, 92.3% for all cancers and 94% for Stage I and II cancers versus 70% for FIT.

Cologuard cancer sensitivity was maintained throughout the colon, and it remained more sensitive than FIT, the sensitivity of which was lower in the proximal colon.

Cologuard detected advanced adenomas, particularly, with good sensitivity; nearly 70% for the subgroup with high-grade dysplasia, the most ominous subgroup, and 42.4% sensitivity for sessile serrated adenomas. Cologuard's overall sensitivity for advanced adenomas was higher than that of FIT.

Cologuard specificity met the primary endpoint and is a

reasonable value given its test sensitivity. It is important to note that the specificity was nearly 90% among the subgroup with clean colons, which was on target with the pre-study estimate.

Finally, Cologuard is safe and simple to use.

In considering the risk/benefit profile, the risks of Cologuard or its false positive and false negative results, these are outweighed by the benefits that include high sensitivity for early stage cancer; sensitivity throughout the colon; the ability to detect advanced adenomas, particularly the most sinister subgroups; and a reasonable balance of test characteristics and ease of use.

Sandy Statz, of Exact Sciences, will now discuss the post-approval study. Thanks for your attention.

MS. STATZ: Good morning. I'm Sandra Statz, and I am vice president of clinical, quality and regulatory for Exact Sciences.

Exact Sciences is proposing to conduct a prospective, longitudinal post-approval study, the objective of which is to evaluate performance of Cologuard at three years as compared to baseline. The study will enroll individuals who are at average risk for colorectal cancer screening. It will be a multicenter trial, and we anticipate requiring a minimum of 20 sites to enroll the approximately 1800 subjects within the first year.

As outlined on this slide, all patients enrolled in the study would take a Cologuard test at baseline. If that result were positive, the

patient would continue to colonoscopy and then be discontinued from the study. Patients with negative Cologuard results will continue in the study, and Cologuard would be repeated at the third year.

As a safety measure for patients continuing into the third year, each would be assessed at the first and second annual time point by the enrolling physician to ensure that there is no change in their medical status related to colorectal cancer that would warrant further investigation.

Following completion of the Cologuard test at Year 3, and regardless of the outcome of that test, all subjects would then proceed to colonoscopy and their participation in the trial would be ended.

The primary endpoint of this study is to look at the risk of colorectal cancer and advanced adenoma among those subjects with positive Cologuard test results at Year 3 as compared to baseline. We expect that the proportion of true positives will be lower at Year 3 because the test would have correctly identified true positives at baseline.

Secondary endpoints would include an assessment of the distribution of colorectal epithelial lesions among subjects with positive results at both time points, and to compare those distributions to those of the DeeP-C study to assess consistency of the positive result distribution. Additionally, we would measure the positive predictive values at both time points. We would also look at the rate of no Cologuard result obtained from the test, and continue to assess the adverse event risk.

So the purpose of this study is that it would provide data to inform questions around the Cologuard interval by assessing positive outcomes at Year 3 as compared to baseline. Specifically, the assessment of the positivity at Year 3 as compared to baseline would provide insight into the appropriateness of a three-year interval, in that a lower positive predictive value may indicate that Cologuard lowers the prevalence of colorectal cancer and advanced adenomas. Conversely, a higher positive predictive value would suggest that patients would benefit from more frequent screening.

Although the study is not designed to provide data sufficient to definitively define the interval, it would allow for a preliminary assessment and lend justification for future longitudinal studies.

Thank you.

I would now like to introduce Dr. Sidney Winawer, who will discuss the Cologuard clinical benefit.

DR. WINAWER: Thank you. I'm Sidney Winawer. I am a gastroenterologist at Memorial Sloan Kettering Cancer Center, where I hold the Paul Sherlock Chair.

I have no equity in the company. I'm on a medical advisory board for which I am compensated, and I am reimbursed for my travel here. I have no financial interest in the outcome of this meeting.

In 2008, the U.S. Preventive Services Task Force gave colorectal cancer screening a Grade A recommendation based on its strongest evidence

and stated that it recommends screening for colorectal cancer using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults beginning at age 50 and continuing for routine screening until age 75, and stated also, very importantly, that the risks and benefits of these screening methods vary.

Screening options have been recommended by many guidelines committees, and you can see on the left that most of the guidelines committees recommend a menu of options, which are indicated on the lower right-hand portion of the slide. One guidelines committee for the American College of Gastroenterology stated that colonoscopy was preferred. There are variations among the guidelines committees as to the options offered, and the way the options are offered, but it is important to note that most of the guidelines committees recommend a menu and that all of the menus include stool testing.

However, I have sat on many guidelines committees and struggled with the limited data available when new tests are introduced. We also take into consideration the long natural history of the adenoma cancer progression, which you've heard from Dr. Levin.

Expert opinion is used extensively in order to interpret the limited data and incorporate it and integrate it with our other knowledge and concepts of the natural history of the adenoma cancer progression, and the other knowledge that we have about the biology of colorectal cancer.

Modeling has been used extensively, especially more recently.

But modeling was used very early, in 1980, by the American Cancer Society, by David Eddy; and also by the U.S. Multi-Society Task Force in 1997, which I chaired; and most recently very extensively by the U.S. Preventive Services Task Force.

Guidelines are not really etched in stone. We all know that. They are guidelines to the physicians to guide physicians and not a cookbook. And they do change and evolve with time, because we know that new data comes out all the time on these screening tests.

To give you some flavor of how these guidelines developed in terms of the introduction of some of these screening tests, sigmoidoscopy was introduced -- rigid sigmoidoscopy -- well, it was introduced way back in the 1870s, but that was kind of like a medieval torture chamber. But the most recent rigid sigmoidoscopes were introduced in 1948 with the very pioneering studies of Ralph Hertz at the Strang Clinic in New York, and Victor Gilbertsen at the University of Minnesota, who did very large, extensive screening studies. But they were point-in-time studies.

The first evidence-based ACS guidelines came out in 1980, many years later, recommending sigmoidoscopy every year for two years and, if negative, then three to five years. And over a period of time, those guidelines evolved so that the recommendation and requirement for the first two negatives were dropped. And then after a baseline sigmoidoscopy, the recommendation was to have it three to five years; and in further evolution

of the guidelines, the recommendation was five years. And now the definitive studies that were reported recently, in 2010 and 2013, which were very large randomized trials with a mortality and incidence -- mainly mortality endpoints -- evaluated the 10-year interval for screening sigmoidoscopy. So you can see how that guideline has -- that has not been yet incorporated into a guideline, in terms of that interval, but we can see from that history how the guideline has evolved.

Similarly, in guaiac-based fecal occult blood tests -- that was introduced in 1967 by David Greegor, who was an internist working out of his office who gave patients the newly available guaiac cards to his patients, and then if it was positive, he got a barium enema out of the patients, which was available at that time and colonoscopy was not available. And he demonstrated early cancer detection by that method. And the guidelines were not developed until 1980, when stool blood testing on an annual basis was recommended.

But the effectiveness studies for the annual interval for stool blood testing did not occur until the report of a series of three randomized trials from the United States and from Europe, which were reported over the years 1993 to 1996, which really validated the effectiveness of annual stool blood testing.

Colonoscopy, the most recent screening test, was introduced in 1970 at the clinical practice, and it was very cumbersome initially and got

much better with time. But the early studies of the National Polyp Study, reported in 1993, indicated that when polyps were identified and removed, the incidence of colorectal cancer was reduced, the expected over observed. And as a result of that, in 1997, the guidelines committee which I chaired recommended screening colonoscopy for the first time, introducing that into the armamentarium of screening options.

Additional studies went on after that to look at the interval of testing. The first interval that was recommended in 1997 was really based on short-term follow-up in the National Polyp Study in a post-polypectomy setting, not a screening setting, and the screening study of Joe Selby at Kaiser, which was a rigid sigmoidoscopy screening study.

So you can see how all of this indirect evidence led to the guidelines in 1997, which introduced screening colonoscopy and also recommended a 10-year interval. The 10-year interval has been challenged, but there are many studies that have seemed to validate that based on observational studies, which have some issues. But the definitive studies with the 10-year interval are still ongoing, and there are three randomized trials, which you've heard about, which will be reported in the 2020s and will validate or not validate the 10-year interval.

So this gives a flavor of how guidelines really evolve over time, the limited data that's available initially, and how they evolve with increasing data as time goes on.

There's been a paradigm shift in our understanding of how to screen for colorectal cancer and what our goals of screening really should be. Initially, the goal was early stage cancer detection, but now the bar has been set higher and the paradigm has been shifted. We now understand that we should be screening for early stage colorectal cancer and for the detection and removal of advanced adenomas in order to prevent colorectal cancer. This was based initially on the National Polyp Study incidence reduction and more recently a report by my colleague, Dr. Zauber, who was the co-PI of the National Polyp Study, a reduced mortality from finding and removing these adenomatous polyps. So it's not an over-diagnosis bias. These are potentially lethal cancers that are identified.

Unfortunately, the stool blood tests that are currently available for noninvasive testing have a very low sensitivity for early stage cancer and a low sensitivity for advanced adenomas. As a result of that low sensitivity, there is a need for a program of annual testing to make up for that deficiency, and that's recommended in all the guidelines.

Unfortunately, there is poor adherence to annual testing, so that first opportunity that we have with a patient with a screening encounter, whether it's in an office or a clinical setting or wherever it is, is where we have to take that opportunity to provide the highest sensitive test.

So where does Cologuard -- what is the place of Cologuard in the screening armamentarium? Well, you've heard from Dr. Levin about the

performance of the invasive tests -- I will not review that again -- and the noninvasive tests. So you can see the performance of FIT and guaiac, the Hemoccult guaiac-based test and the old Hemoccult II test, and you can see where the place of Cologuard is. It really dominates the noninvasive tests in terms of sensitivity for colorectal cancer and sensitivity for advanced adenomas, and as you heard before -- and not on this slide -- the sensitivity for high-grade dysplasia, which is the bridge between the advanced adenoma and invasive cancer. High-grade dysplasia really is cancer. It used to be called in situ cancer. It's just not invasive through the muscularis. We don't call it in situ cancer anymore because we don't wish to trigger off clinical decisions to operate on these patients because they're cured when the high-grade dysplasia is removed.

So what is the clinical use of Cologuard, and how does it fit into our understanding of the guidelines? Well, average-risk screening patients who are eligible should be offered a menu of options. This varies, and some physicians will make a single recommendation. In other healthcare settings, a menu will be recommended. And yet another healthcare setting, stool-based testing will be recommended. But it's important to have the menu available for all of these options. And then these can be recommended and Cologuard can be added to this. And if positive, the patient should be referred to diagnostic colonoscopy, as for any other of the screening tests. And if negative, the patient should discuss future screening with the physician, in

terms of the menu of options that are available.

So what are the potential clinical benefits of Cologuard? Well, it adds to the menu of screening options. Guidelines recommend offering patients the choice of both invasive and noninvasive screening modalities. Cologuard would provide a new noninvasive option with a different performance profile.

It has a higher sensitivity than current noninvasive tests, as you've heard. So it's important for the initial screening to be high sensitivity because the adherence to sequential testing, we know, has been imperfect. Cologuard demonstrated significantly higher sensitivity than FIT, the leading noninvasive test. I think it's the best of the noninvasive tests.

It addresses the new colorectal cancer screening paradigm. We are setting the bar higher for cancer and advanced adenomas, not just cancer. The screening goal is to reduce mortality by detecting early stage cancer and also reducing cancer incidence by detecting and removing pre-cancer. Cologuard has high early stage cancer sensitivity and clinically meaningful pre-cancer sensitivity. So it really fits very well into our understanding of what the current paradigm of screening should be.

So on a personal note, the goal of all of us here today really is to help avoid the 50,000 deaths of men and women in this country each year, and to prevent many of the 130,000 new cases of colorectal cancer in men and women in this country each year. Many of you, like me, who have been

touched by cancer, fully understand the human value of these goals.

Thank you.

MR. CONROY: That concludes the Sponsor's presentation. Thank you very much for your time and attention. And thank you to the FDA and also to CMS for all of the efforts put into the design of the study.

DR. PRZYGODZKI: I would like to thank the Sponsor, as well as his representatives, for the presentations.

I would like to give the Panel 15 minutes to ask questions that are brief and just to get greater clarification. Please remember that we also have the afternoon, a specific session, and we'll ask both the Sponsor as well as FDA for further clarifications.

Are there questions that the Panel Members have at this point?

DR. McSHANE: Lisa McShane, NCI.

Could the Sponsors please describe for us the process of locking down the model that was used? Specifically, I know there was some subset of over 1,000 cases -- I think it was -- that were used to refine the model and set cut points. And so can you tell me what the origin of those samples were versus the samples that were used in this pivotal trial that you discussed, and assure me that there was no interplay between those two things and your documentation of the lockdown? If you could describe that process for me.

DR. LIDGARD: Certainly. Graham Lidgard, Exact Sciences.

Dr. McShane, the cutoff study was done under three different clinical trial protocols that are on ClinicalTrials.gov. One was collecting advanced adenomas and colorectal cancers from people who had been diagnosed with colorectal cancer. And the stool sample was collected 7 to 10 days after but prior to any surgical removal of the tumor or adenoma. For the normals, most of them were collected post-colonoscopy and had no resectable lesions taken.

There was another small study that was a study of pre-colonoscopy samples that were determined to be normal after colonoscopy. All of those samples were combined into a study. None of those samples overlapped at all with DeeP-C. They had nothing to do with the DeeP-C study.

So those samples were used in an analysis. They were tested blind. And when the code was broken, we ran different algorithms; we looked at all different processes on the algorithm, and we came up with a logistic regression algorithm with a number of small additional pieces.

For example, if a sample is less than 10 strands for any target, we call that zero. It was invalid if the amount of DNA was $<$ 200 strands in the sample. And we also used high boundary conditions for the molecular markers, from the point of view of if the molecular marker was above 99.5% of the normal range, we added an additional factor to push that into the abnormal range.

So, overall, the algorithm was developed. It was tested statistically with various statistical methods of "leave one out"; 10% of the population/1,000 iterations. We developed a precision profile for every marker and used that to estimate what the precision and what the reproducibility was at each different level of marker. Once that had been fixed, the algorithm was programmed into software and it was locked into the software and communicated to the FDA before we even began testing for DeeP-C samples.

DR. SKATES: My question -- this is Steven Skates -- has to do with setting the goals for the primary endpoints and the secondary endpoints for the study, and particularly, there was a balance between sensitivity and specificity that was chosen. I would just like to understand how that choice of 85% specificity came up. Why wasn't it 90% or 97% or 95% like the FIT test had? And that relates to why wasn't, in the secondary endpoints, a goal of at least comparability in specificity with the FIT test, why was that not set? And the reason there being that sensitivity and specificity are tradeoffs and combined to summarize the characteristics of a screening test.

DR. IMPERIALE: That's correct. Exactly as you state, Dr. Skates, there's a tradeoff between sensitivity and specificity. So to allow optimization of sensitivity, we had to give a little bit on specificity but still felt that 85% was a reasonable goal based on interviews done with primary care docs for what a reasonable level of specificity would be.

DR. SKATES: So it was primary care physician groups that weighed in on what they thought was a reasonable --

DR. IMPERIALE: A reasonable limit.

DR. SKATES: -- false positive rate?

DR. IMPERIALE: Yes.

DR. SKATES: Okay.

MS. DeLUCA: Jo-Ellen DeLuca, Patient Representative.

I'd like to ask if this is a test that could be used publicly, not just in the doctor's office -- say, at the CVS clinics that are now popular or with DHEC or public health clinics that are out in the community, say, in rural areas.

MS. STATZ: Sandra Statz, Exact Sciences.

The kit used is prescribed by a doctor or a healthcare provider with the ability to do so, and then it is sent to a patient's home. So in terms of reaching patients in rural areas, it can be distributed as such. The kit is just returned to the clinical lab through a shipping method that will be established.

DR. LIPKIN: Hi. Thank you.

I think you guys did a very thorough presentation, and I congratulate you actually on a number of very large and very well-performed trials and a very nice background of the field.

I had a couple quick questions. The first is to Drs. Ahlquist and

Imperiale about blinding.

I just wanted to clarify: In the patients who were enrolled and the subjects who tested and were positive and negative, these were all patients under screening colonoscopy. There were no surgery patients.

The question is, is there an issue, potentially unconscious blinding or unblinding of samples from patients who had been diagnosed with colon cancer?

DR. IMPERIALE: I want to make sure I understand your question. I can tell you up front that all of the specimens were processed blinded to the colonoscopy results, and they were actually all processed after all the patients were entered into the study.

DR. LIPKIN: So the people at the primary sites who took the stool samples and put it into FedEx, or whatever it is you used to send it --

DR. IMPERIALE: Right.

DR. LIPKIN: -- did not know the status and were blinded in every case?

DR. IMPERIALE: Absolutely. And the FIT test and Cologuard were processed independently of each other by separate labs.

DR. LIPKIN: Okay, thank you. I think that's important.

Another quick question. You have the actin -- this is, I guess, a question to Dr. Lidgard.

The test includes a positive control that is important for

assessing quality -- actin, right?

DR. LIDGARD: Yes.

DR. LIPKIN: Yes.

So your test combines both genetic and epigenetic aspect tests, really, right?

So the actin test -- the question is, what are your positive controls so that we know that the methylation is actually working well? The methylation analyses -- excuse me.

DR. LIDGARD: We used three controls in the actual assay itself. These are controls that have high methylation, low methylation, and negative samples, and those are run in the assay, along with the clinical samples, during the process.

DR. LIPKIN: So the actin helps to ensure the integrity of the DNA, that you can detect it and you can use it, but there's no internal control for any methylation?

DR. LIDGARD: Well, the actin is an internal control in the sense that it's both a patient control and an internal control. At the actin level, it is less than 200 strands. That could be due to the assay processing or it could be due to the clinical sample. We don't differentiate it at that stage. The sample is invalid and a repeat of that sample or a second sample is requested.

DR. LIPKIN: Okay, thank you.

Just a related question, thinking -- and this came up. And I

realize that this is separate from the Panel yesterday, but this is an issue that came up, about the issue of age-related change in DNA methylation.

Yeah, this would be for you again, thank you. Sorry.

So the question is about potential age restrictions or warnings about individuals, because we know that DNA methylation abnormalities do occur in older individuals, and this is part of the natural biology and you would anticipate it. And I think, when I looked the data, that there seemed to be reduced specificity with increasing age, which is at least a separate application, something at least we addressed or even saw in the literature yesterday.

DR. LIDGARD: Yes. In the initial studies that we did, we actually published the age specificity and age effect of methylation, and we selected markers that have minimal effect on age. We eliminated markers that had elevated with age.

But I'll leave that to Dr. Itzkowitz to talk about -- the clinical significance of that.

DR. ITZKOWITZ: Good morning. My name is Dr. Steven Itzkowitz.

I am a professor of medicine, and I am also the director of the gastroenterology fellowship training program at the Icahn School of Medicine at Mount Sinai in New York City.

As a disclosure, I was an investigator on the DeeP-C study, and

my institution was compensated for my time. I'm also a scientific advisor to Exact Sciences, and my institution has been compensated for that work. I'm being reimbursed for my travel here today, but I do not hold any equity interest in the company, and I have no financial interest in the outcome of this meeting.

You raise an important point about the specificity going down with age.

Could I have the first slide?

And this shows what Dr. Imperiale indicated, and that is, as you get older there is a decrease in specificity, meaning that there are more false positives. However, the sensitivity of the assay for detecting colorectal cancer, as you see in this slide, is consistent even in the older age groups. So although specificity may decline, the sensitivity is constant.

And, importantly, because the prevalence of colon cancer goes up with age, if you then look at the positive predictive value for colorectal cancer as a function of age, you actually see that the positive predictive value is not only sustained, but it is actually increased in the older population.

DR. PRZYGODZKI: Dr. Weck.

DR. WECK: Yes, I have a question for Dr. Lidgard also, regarding the mathematical algorithm.

So, first of all, I just wanted to thank all of the presenters also for the very well-done work. And I'm excited about the data of sensitivity as

a potential screening assay.

I did have one question about the mathematical algorithm, which you derived via linear regression -- and we were provided it in our Executive Summary. So I don't see it, however, in the package insert for laboratories. So I assume that it's going to remain proprietary information. And would this then be considered a black box multivariate index analysis assay?

DR. LIDGARD: We've recently published the DeeP-C data and it's available online in the *New England Journal.*

DR. WECK: In the *New England Journal* article, okay.

DR. LIDGARD: And in the supplemental information, the algorithm is available.

DR. WECK: Got you, okay.

DR. LIDGARD: However, within the assay itself, the software does all of the calculation and produces a negative or a positive result, and that's what is reported to the clinician.

DR. WECK: Right, I understand.

Okay, thank you for that clarification.

DR. PRZYGODZKI: Dr. Caggana.

DR. CAGGANA: My question was -- the first part of the question was to further explain the algorithm and how you came to -- you know, how things are weighted, because I noted that the non-bleeding

tumors obviously won't have a score from the hemoglobin. So is that the reason why the sensitivity is lower in that group and they're all weighted the same?

DR. LIDGARD: I'm not sure I fully understand your question. You mean the sessile serrated --

DR. CAGGANA: Yes.

So I'm thinking that the hemoglobin component adds to the algorithm, and because they don't bleed as much, you lower the score and that's why you don't pick those up as frequently. Is that true?

DR. LIDGARD: Well, no. The principal components that obviously are contributing to the sessile serrated polyps is the molecular markers because, as you said --

DR. CAGGANA: Right.

DR. LIDGARD: -- the hemoglobin level is very low.

Within the algorithm itself, it was based on a logistic regression formula which assigns a weight to each individual methylation mutation or hemoglobin result. And then, in a very simple sense, that weight is based on the odds ratio or odds of having a neoplasia in the specimen. And after the weight is applied, all of the multiples of the parameter plus the marker is added together, and that contributes to the Cologuard score. It's exponentiated into an equation so that it gives a 0 to 1,000 score so that the lab can do quality control. But that score is not reported to the clinician.

DR. CAGGANA: Okay, thank you.

DR. PRZYGODZKI: And one final question from me.

Out of curiosity, just for interest's sake, when one looks at the methylation markers versus the mutation markers, which one was more informative in the study?

DR. LIDGARD: Well, as we know, the KRAS mutations are only present in 30% to 40% of colorectal cancer patients. The methylations based on our tissue studies are present in all of the cancer lesions and, in fact, in all of the adenomas. And we also determined that the KRAS mutation is present in about 30% to 40% of the adenomas as well.

So, in relative terms, the methylation is contributing more of the piece, but there are about -- you know, really there are four ways that the parameters come together. You can have an elevated hemoglobin, you can have an elevated mutation, you can have an elevated methylation. So you can have elevated molecular markers or you can have a combination of both -- both moderately elevated -- contributing to a positive score. And that's the benefit of the algorithm, that it combines those levels that are just below the cutoffs into a positive result.

DR. PRZYGODZKI: Excellent, thank you.

At this point we'll take a 15-minute break, and we'll start again at 10 o'clock.

(Off the record.)

(On the record.)

DR. PRZYGODZKI: So it is a little bit past 10:00, and at this point, I would like to call the meeting back into order.

And the FDA will now be giving their presentation.

Again, I'd like to remind the audience that if you have questions, please let me know.

And you have 75 minutes. Thank you.

DR. HUNTER: Good morning.

My name is Nina Hunter, and I am a reviewer in the Office of In Vitro Diagnostics and Radiological Health, in the Division of Immunology and Hematology. Drs. Pennello, Tzou, and I will be giving a joint presentation today to summarize FDA's review of the Exact Sciences Corporation's Cologuard assay for colorectal cancer screening.

Before I begin, I would like to acknowledge that the review of this submission has involved the work of numerous individuals and managers who work within various offices and divisions across our Center. I have listed here some of the key individuals. Dr. Tzou is a medical officer, and Drs. Song, Li, and Pennello make up the statistical team. Other areas of review include software, manufacturing, bioresearch monitoring, analytical, epidemiology, and labeling.

Cologuard is a first-of-a-kind in vitro diagnostic device, which means that no device for the proposed intended use is currently cleared or

approved in the United States. Based on the test performance of Cologuard, we are here today to seek Panel input on the safety and effectiveness of this first-of-a-kind device. We are also seeking input on whether the benefits outweigh the risks of using this device in the context of the proposed intended use. To this end, we ask that the Panel Members please keep in mind the Panel discussion questions as we continue through our presentation.

Our FDA presentation will be divided into three parts. In this first part, I will provide a summary of the regulatory and submission history of this device. I will review for you its proposed indications for use, along with the proposed contraindications, as already introduced to you by the Sponsor. I will then provide a brief overview of the device workflow and summarize for you the analytical studies reviewed by the FDA to support the approval of this device. Finally, I will introduce to you the pivotal clinical study, DeeP-C, that was conducted to support the safety and effectiveness of this device for colorectal screening.

In the second part of the presentation, Dr. Pennello, from our statistical team, will cover statistical analyses that include patient accountability, primary and secondary effectiveness results, secondary objectives, predictive value, and other statistical analyses, including intent to diagnose, age-adjusted sensitivity and specificity, receiver operating characteristics, benefit/risk, and subgroups.

In the final part of our presentation, Dr. Tzou will discuss key aspects of the clinical study as it relates to the FDA questions for Panel discussion. He will also present the post-approval study proposed by the Sponsor, along with additional review and labeling considerations.

This premarket application, or PMA, was submitted in modules such that the contents of a traditional PMA were submitted as well-defined components or modules at the predetermined time points.

The first module was received in December of 2012. With the submission of the final module in July of 2013, the modular PMA was converted to a traditional PMA and assigned PMA Number P130017 and granted priority review status. A major deficiency letter was issued two months later in September, and the Sponsor submitted a formal response to these deficiencies in January of 2014. Any remaining issues are currently being addressed interactively.

In addition, this PMA submission is a pilot for the Agency and Center for Medicare and Medicaid Services, or CMS, Parallel Review Program, which was established for concurrent review of certain FDA premarket review submissions for medical devices and CMS national coverage determinations. The goal of the program is to reduce the interval between FDA marketing approval and medical coverage.

As you've already seen in the Sponsor's presentation, this is the proposed indications for use of Cologuard. I will read it for you here.

"Cologuard is intended for use as an adjunctive screening test for the detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of colorectal cancer or pre-malignant colorectal neoplasia. Cologuard is not intended as a replacement for diagnostic colonoscopy. A positive result in Cologuard, as with any screening test, should be followed by colonoscopy. Cologuard is intended for patients who are typical candidates for colorectal cancer screening: adults of either sex, 50 years or older, who are at average risk for colorectal cancer."

A complete list of contraindications will be listed in the labeling of the device. I will highlight some key proposed contraindications here.

Cologuard is not suitable for everyone. This test is indicated for men and women, age 50 years or older, who are at average risk for development of colorectal cancer. Patients should inform their doctor if they have a history of colorectal cancer, adenomas, or other related cancers; if they have had a positive result from another colorectal cancer screening method within the last six months; if they have been diagnosed with a high-risk condition for colorectal cancer, such as inflammatory bowel disease, chronic ulcerative colitis, Crohn's disease, familial adenomatous polyposis, or have a family history of colorectal cancer; and lastly, patients should inform their doctor if they have been diagnosed with a relevant hereditary cancer syndrome, and a complete list of these syndromes will be included in the

labeling.

The Cologuard device under review includes the Exact Sciences tool collection kit, which includes instructions for use, a bracket to secure the collection device to a toilet, a collection container for stool, a protein sample tube for stool, a bottle of liquid preservative, and a return shipping box. The assay itself contains a series of reagents, controls, laboratory equipment, and instruments and software. The device includes all of these components.

FDA reviewed analytical studies conducted with the collection kit, reagents, and controls as well as current good manufacturing practice documentation for all of these components. A user study was also conducted for the collection kit.

Now I will describe the general Cologuard workflow. The patient will receive a collection kit in the mail. The patient then collects one stool sample in the bucket, scraps off a bit for the protein sampling tube, which includes a scraper in the cap, pours in the entire bottle of liquid preservative into the bucket, and packs the box for shipping to the lab.

When the testing laboratory of Exact Sciences receives a stool collection kit, the kit will be weighed and separated. The stool container will be used for molecular testing, while the protein sample will be used for hemoglobin testing. This means that each will go through a different workflow but that the separate results will be combined at the end to determine a reportable result, positive or negative.

The molecular part of the assay begins with target-specific capture to isolate DNA from frozen stool homogenates. The captured DNA is then split here into two portions, one for bisulfate conversion of methylated DNA and one for DNA purification. Then both are combined for quantitative allele-specific real-time target and signal (QuARTS) amplification, which combines real-time PCR and invasive cleavage chemistry to perform allele-specific amplification and detection of methylated target DNA, specific DNA point mutations, and total human DNA.

In parallel, a quantitative ELISA, or an enzyme-linked immunosorbent assay test that uses antibodies and color changes to identify a substance, is conducted to analyze levels of hemoglobin present in the stool sample. From here on out, the ELISA-based portion of the assay will be referred to as FIT, or F-I-T, for fecal immunochemical testing.

As you see here, there are three distinct, independent families of markers assayed in Cologuard. More specifically, the assay looks for epigenetic changes in the form of gene promoter region hypermethylation and a promoter DNA region of two genes, NDRG4 -- for N-myc down-regulated gene 4 -- and BMP3, for bone morphogenetic protein 3. For specific point mutations, seven DNA mutations in codons 12 and 13 of the Kirsten rat sarcoma viral oncogene homolog, also known as KRAS, are assayed. Hypermethylation of NDRG4 and BMP3, as well as point mutation and the KRAS, are all thought to be associated with colorectal cancer. Fecal

hemoglobin is assayed in the non-molecular portion of the assay, and beta-actin is used as a reference gene to estimate the total amount of human DNA in each sample as a control.

The last part of Cologuard includes an algorithm which combines the weighted results from each of the analytes to generate a composite score between 0 and 1,000. And if that composite score is equal to above the cutoff of 183, the assay will report positive. If the composite score is below the cutoff of 183, the assay will report negative. No numbers will be reported for the assay.

In terms of analytical studies conducted to support the approval of Cologuard, in most cases each individual analyte from each of the three families of markers were independently assessed in these studies.

The following studies were conducted by the Sponsor: analytical sensitivity, which included limit of detection, limit of quantitation, limit of blank, and linear range and linearity; analytical specificity, which included double KRAS mutation, partially methylated targets, wild-type KRAS, and cross-reactivity; interfering substances, carryover, and cross-contamination; development and validation of the Cologuard algorithm and cutoff; precision and reproducibility, which included lab-to-lab and lot-to-lot; robustness; serial stool study; analytical specificity to other cancers; and shelf-life and packaging studies.

In all, FDA reviewed the analytical data submitted to support

the safety and effectiveness of Cologuard and found them to be acceptable.

And now, in terms of clinical data, the Sponsor conducted a clinical study called DeeP-C to support the safety and effectiveness of Cologuard. The DeeP-C pivotal study began enrollment in June of 2011 and ended in February 2013. Ninety enrollment sites were made up of primary care point-of-referral sites and colonoscopy centers. Eighty-nine of these sites were in the U.S. and one is in Canada. A total of 12,776 patients were enrolled, and enrollment was enriched with patients ages 65 to 84, which accounted for about 64% of patients in the study.

The study was designed to collect cross-sectional data, meaning that data was collected from a population at one specific point in time. Patients were required to have colonoscopy within 90 days of sample collection, and as recommended by the FDA for this clinical trial, patients were asked to also include some stool in a separate collection tube for a head-to-head comparison to a currently marketed representative FIT.

The Polymedco FIT was chosen as the FIT for this clinical study because of two reasons. First, the Sponsor understood it to be the best performing FIT test at the time, based on the information available; and at the time the study was developed, several large healthcare providers had recently switched to use the Polymedco FIT based on the independent analyses. And, second, it is the most commonly used FIT in the U.S. The Sponsor understood that over the past five years it had evolved to have

greater than 50% market share among FIT tests. And according to the DeeP-C study results, the performance of the Polymedco FIT in the DeeP-C is generally in line with what would be expected per literature. These results will be shown later in the FDA presentation.

After stool collection for Cologuard and the Polymedco FIT, clinical trial samples were analyzed at one of three testing labs. During the testing, the evaluators of Cologuard, FIT, and biopsy histology were mutually masked to the other results. Lastly, the results were not used for clinical management of these patients.

Results were compared to colonoscopy, and histopathology was performed on any biopsied or excised lesions. Histopathology analysis was performed first by a local pathologist to guide treatment decisions for the patient. Histopathology reports were then reviewed by an independent central pathologist, as part of the study, to confirm diagnosis and to characterize patients for the study.

Patients were characterized for the study as such: Category 1 for colorectal cancer Stages I through IV; Category 2 for advanced adenoma; Categories 3 through 5 for adenomas; and Category 6 for negative or no neoplastic finding, either 6.1 for negative upon histopathological review or 6.2 for no finding on colonoscopy and therefore there was no histopathological review.

Here are the inclusion criteria for DeeP-C. The patient was at

average risk for development of colorectal cancer, the patient was between 50 and 84 years of age, and the patient had not had a colonoscopy in the previous nine years.

I will highlight some of the key exclusion criteria here. The patient did not have any condition that in the opinion of the investigator should preclude participation in the study; the patient did not have a history of colorectal cancer or advanced adenoma or aerodigestive tract cancer; the patient did not have a prior colorectal resection for any reason other than sigmoid diverticular disease; the patient did not have overt rectal bleeding within the previous 30 days; the patient did not have a diagnosis or personal history of any high-risk conditions for colorectal cancer, or of any other high risk for colorectal cancer per family history.

To evaluate the performance of the clinical study, the Sponsor pre-specified the following primary and secondary objectives.

The first primary objective was that Cologuard sensitivity for colorectal cancer shall have a one-sided 95% lower confidence bound of ≥ 65%. So Cologuard sensitivity for colorectal cancer or those patients in Category 1 shown in the table.

The second primary objective was that Cologuard specificity for Categories 3 through 6 shall have a one-sided 95% lower confidence bound of ≥ 85%; so Cologuard specificity for patients in Categories 3 through 6 in the table.

The Sponsor considered all non-colorectal cancer findings, including advanced adenomas in Category 2, to be true negatives such that only subjects in Categories 3 through 6 were included in the specificity analysis.

Here are the Sponsor's pre-specified secondary objectives. They are that Cologuard shall be non-inferior to FIT for colorectal cancer sensitivity, with respect to 5% non-inferiority margin, and that Cologuard shall be superior to FIT for advanced adenoma sensitivity.

And with these pre-specified performance criteria, Dr. Pennello will now present the statistical performance evaluation of the clinical study.

DR. PENNELLO: Good morning, Panel.

My name is Gene Pennello, and I'll be giving the FDA's statistical presentation today. In the presentation, I'll provide some results from statistical analysis of the data from the DeeP-C clinical pivotal study.

And I'd like to acknowledge Kyunghee Song, the lead statistical reviewer for this submission, and Qin Li and other FDA statisticians who helped with the review.

In the talk, I'll present an accountability of subjects in the study; primary and secondary effectiveness results; Cologuard classification accuracy, that is, sensitivity and specificity; and predictive value of CRC and advanced neoplasia and other statistical analyses listed here.

In the pivotal study 12,776 subjects were enrolled. For several

reasons, a number of subjects were excluded from the primary effectiveness population. For some subjects, a histopathological diagnosis was not available because, as indicated, the subject withdrew consent, did not undergo a colonoscopy, or had an unusable colonoscopy. Additionally, for some subjects, the Cologuard result was not available because the stool sample was not collected, was untestable, was not analyzed, or because the test result was invalid.

A total of 2,753 subjects were excluded. Thus, the primary effectiveness population consisted of the remaining 10,023 subjects with a valid histopathological diagnosis and a valid Cologuard result. The secondary effectiveness population consisted of 9,989 subjects who additionally had a valid result from the Polymedco FIT test.

As a reminder, the histopathological categories are listed on this slide. Category 1 is the diagnosis of CRC. Category 2 is advanced adenoma, or AA; and advanced neoplasia, or AN, as defined as either CRC or AA. Thus, in this talk, Categories 3 through 6 are considered together as non-AN.

For a diagnostic test that yields a binary result -- test negative or test positive for a disease of interest -- a pair of performance measures, sensitivity and specificity, evaluate the ability of the test to correctly classify diseased and non-diseased subjects, respectively. If the disease is CRC, then sensitivity is the proportion of CRC subjects (Category 1) who test positive,

and specificity is the proportion of non-CRC subjects (Categories 2 through 6) who test negative.

If the disease is AN -- that is, CRC or AA -- then sensitivity is the proportion of AN subjects (Categories 1 and 2) who test positive. And AN specificity is the proportion of non-AN subjects (Categories 3 through 6) who test negative.

Note that both pairs -- sensitivity and specificity for CRC and sensitivity and specificity for AN -- are complementary and that they span the entire study population; that is, the entire spectrum of disease is considered. In contrast, if some study subjects are excluded from a sensitivity/specificity pair, such that the remaining subjects are not representative of the entire disease spectrum, then a spectrum effect or a spectrum bias is introduced.

In the study protocol, the primary performance measures are defined as CRC sensitivity and AN specificity, as indicated by the superscripted daggers. This pair of measures is not complementary in that AA subjects are excluded from both measures. The Sponsor elected to exclude AA subjects from the specificity measure, in our understanding, because AA is treated during colonoscopy and therefore can be considered a positive outcome, in that sense. Instead, AA is considered separately as a secondary analysis, in a secondary analysis of AA sensitivity.

Because AA is excluded from the primary performance measure pair of CRC sensitivity and AN specificity, a spectrum bias is introduced into

this pair regarding classification performance. Because of this concern, FDA had requested that the Sponsor also evaluate CRC specificity as a complement to CRC sensitivity. To aid in the interpretation of study results, the two complementary pairs -- sensitivity and specificity for CRC and sensitivity and specificity for AN -- will be presented, as well as the primary and secondary performance measures.

The pre-specified primary objectives for the study were that the one-sided 95% lower confidence bounds on CRC sensitivity and AN specificity exceed the performance goals of 65% and 85%, respectively. In contrast, in other medical device submissions, the level of evidence is that the study goal is met with a two-sided 95% confidence interval, or CI. The two-sided 95% CI is a higher level of evidence and will also be presented for some analyses.

Results on the primary effectiveness population are summarized in this contingency table. In the table, the Cologuard binary test result is cross-classified by histopathological categories of CRC, AA, and non-AN. Within each category, the distribution of the Cologuard result is given in parentheses. These data can be used to analyze the primary objectives of the study.

Results on the secondary effectiveness population are summarized here with three contingency tables for CRC, AA, and non-AN. Each table cross-classifies Cologuard binary test result with the Polymedco FIT

binary test result. These data can be used to analyze the secondary objectives of the study.

Results on the pre-specified analyses will now be presented.

For the primary performance measure of CRC sensitivity, the estimate was 92.3%. The one-sided 95% lower confidence bound was 84.5%, which is greater than the study goal of 65%. Thus, the pre-specified study goal was met for CRC sensitivity.

For the primary performance measure of AN specificity, the estimate was 86.6%. The one-sided 95% lower confidence bound was 86.0%, which is greater than the study goal of 85%. Thus, the pre-specified study goal was met for AN specificity.

Recall that in the DeeP-C study, 817 subjects in the primary effectiveness population were missing a valid Cologuard result and were therefore excluded from the analysis.

The reasons for why the Cologuard result was missing are listed again on this slide in red.

To assess if study conclusions were robust in missing Cologuard results, FDA performed an intention-to-diagnose, or ITD, analysis. For diagnostic tests, a full ITD analysis includes every subject, regardless of whether the subject is missing the test result, the clinical reference diagnosis, or other test results from comparators. In a limited ITD analysis, subjects with missing Cologuard results were included. The missing test results were

imputed, assuming they were missing at random, a commonly made statistical assumption.

In the ITD analysis, the estimate for CRC sensitivity is 92.3%, and the one-sided 95% lower confidence bound (84.5%) was unchanged from the original analysis. Furthermore, the two-sided 95% CI was 83.0% to 97.5% and is also > 65%. Therefore, in the ITD analysis, the study goal for CRC sensitivity was met with the two-sided 95% CI, as well as the pre-specified one-sided 95% lower confidence bound.

The estimate for AN specificity was 86.6% with a one-sided 95% lower confidence bound of 86.0%. Furthermore, the two-sided 95% confidence interval was 85.9% to 87.3% and is > 85%. Therefore, in the ITD analysis, the study goal for AN specificity was met with a two-sided 95% confidence interval, as well as the pre-specified one-sided 95% lower confidence bound.

A pre-specified secondary objective was to demonstrate that Cologuard is non-inferior to FIT in CRC sensitivity with respect to a non-inferiority margin of 5%. The estimate of CRC sensitivity was 92.3% for Cologuard and 73.9% for FIT. The difference is 18.4%. To assess the non-inferiority goal, a two-sided 95% confidence interval on the difference is used here. The two-sided 95% CI was 5.9% to 31.5%, which is > -5%. Thus the study goal, that Cologuard is declared non-inferior to FIT in CRC sensitivity, was met.

Because Cologuard was declared non-inferior to FIT in CRC sensitivity, the Sponsor also evaluated Cologuard for superiority to FIT in CRC sensitivity. Because the two-sided 95% CI is > 0%, Cologuard could be considered superior to FIT in CRC sensitivity.

Another pre-specified secondary objective was to demonstrate that Cologuard is superior to FIT in AA sensitivity. The estimate of AA sensitivity was 42.4% for Cologuard and 23.8% for FIT. The difference is 18.6%. The two-sided 95% CI was 15.3% to 22.1%, which is > 0. Thus, the study goal, that Cologuard is declared superior to FIT in AA sensitivity, was met.

The complementary pair performance of measures of sensitivity and specificity for CRC will now be considered. This pair considers advanced adenoma (AA) as disease-negative. Therefore, AA contributes to the calculation of CRC specificity.

The two-sided 95% confidence interval on sensitivity and specificity for CRC may be compared against the study goals of 65% sensitivity and 85% specificity. For CRC sensitivity, the estimate was 92.3%. The two-sided 95% CI is greater than the study goal of 65%. Thus, the study goal of 65% for CRC sensitivity was met with a two-sided 95% CI.

For CRC specificity, the estimate is 84.4%. The two-sided 95% confidence interval has a lower bound of 83.7%, which is less than the study goal of 85%. Thus, the study goal of 85% specificity was not met if it is

applied to the CRC specificity.

In the DeeP-C study, subjects age 65 to 84 were enrolled preferentially, with 63% of subjects enrolled in this age group compared to only 36.7% in the 2010 U.S. census population, as indicated here. Because of the disparity, FDA performed an analysis of sensitivity and specificity for CRC that adjusts the estimates to the 2010 U.S. census age distribution.

For a comparison, the estimates of CRC sensitivity and CRC specificity observed in the study, and their two-sided 95% confidence intervals, are shown. The age-adjusted estimates are boxed in red. For CRC sensitivity, the age-adjusted estimate was 90.9%, smaller than the original estimate of 92.3%. The two-sided 95% confidence interval was 79.3% to 97.6%, which exceeds the study goal of 65%. Thus, the study goal was met for CRC sensitivity in this age-adjusted analysis.

For CRC specificity, the age-adjusted estimate was 85.8%, greater than the original estimate of 84.4%. The two-sided 95% confidence interval has a lower bound of 85.0%, which is equal to the study goal of 85%. Thus, the study goal was just met if it was applied to CRC specificity in this age-adjusted analysis.

The complementary pair of performance measures, AN sensitivity and AN specificity, was also considered. This pair considers AA as disease-positive because advanced neoplasia is defined as CRC or AA. Therefore, AA contributes to the calculation of AN sensitivity.

The two-sided 95% confidence intervals on sensitivity and specificity for AN may be compared against the study goals of 65% sensitivity and 85% specificity. For AN sensitivity, the estimate was 46.3%, which is less than the study goal of 65%. Thus, the study goal of 65% is not met if it is applied to AN sensitivity.

For AN specificity, the estimate is 86.6% with a two-sided 95% lower bound of 85.9%, which is greater than the study goal of 85%. Thus, the study goal of 85% for AN specificity was met.

Estimates age adjusted to the U.S. census population were obtained for the complementary pair of sensitivity and specificity for AN and are boxed in red. The conclusions are the same as for the unadjusted estimates. The study goal for 65% sensitivity was not met if it is applied to the age-adjusted AN sensitivity. The study goal of 85% specificity was met for age-adjusted AN specificity.

The predictive value of Cologuard positive and negative test results are now considered.

In this table, the predictive value of negative and positive Cologuard test results are given for CRC, AA, and non-AN Categories 3 through 6 in the primary effectiveness population. The positive predictive value -- or PPV -- was 3.72% for CRC, 20.0% for AA, and 76.3% for non-AN.

The PPV of 3.72% for CRC is the proportion of subjects with a positive Cologuard test result who have CRC. In contrast, the prevalence of

CRC, which I'm denoting here as the pre-test predictive value, was .65% in the study. Thus, a subject with a Cologuard positive test result was 5.7 times more likely to have CRC than a subject randomly selected from the overall study population.

The PPV for AA was 20%. It is the proportion of subjects with a positive Cologuard test result who have AA. In contrast, the prevalence of AA was 7.6%. Thus, a subject with a Cologuard positive test result was 2.6 times more likely to have AA than a subject randomly selected from the overall population.

The negative predictive value, or NPV, for non-AN Categories 3 through 6 was 94.7%. In contrast, the prevalence of non-AN was 91.8%. In other words, the proportion of subjects with a negative Cologuard test result who have AN, either AA or CRC, was 5.3%, while the prevalence of AN in the study was 8.2%. Thus, a subject randomly selected from the overall population is 1.6 times more likely to have AA or CRC than a subject with a Cologuard negative test result.

In this slide, Cologuard is compared with the Polymedco FIT test on negative and positive predictive values for CRC, AA, and non-AN in the secondary effectiveness population. The PPV for CRC is smaller for Cologuard (3.72%) than for FIT (6.86%). The PPV for AA is also smaller for Cologuard (20.0%) than for FIT (25.7%). However, the NPV for non-AN is larger for Cologuard (94.7%) than for FIT (93.6%). In other words, 5.3% of Cologuard

negative subjects had AN, while 6.4% of FIT negative subjects had AN, a 21% increase.

To further evaluate Cologuard classification of CRC and non-CRC subjects, ROC analysis was considered. In general, ROC analysis evaluates the ability of a test to discriminate between diseased and non-diseased populations of subjects. This slide displays hypothetical distributions of a continuous value test result in diseased and non-diseased subjects.

For each threshold or cutoff in the test result, it confers a true positive fraction, or TPF, and a false positive fraction, or FPF, for the test, that is, sensitivity and 1 minus specificity. On an ROC plot, FPF and TPF are plotted as a point with FPF as the abscissa and TPF as the ordinate. For a particular threshold, shown on the left, FPF and TPF both equal one. This point is plotted on the right. For another threshold, another point of FPF/TPF is conferred. If the threshold is varied across the entire range of observed test results, all the FPF/TPF pairs can be plotted, resulting in an ROC plot for the test.

Ideally, the ROC plot passes through the upper left corner where FPF=0 and TPF=1. Qualitatively, the closer the plot is to the upper left corner, the higher the overall accuracy of the test.

In the CRC ROC analysis, the ROC plots for Cologuard and Polymedco FIT were compared. In addition, the ROC plot was drawn for the

FIT component of the Cologuard algorithm, which is denoted as EXACT FIT. On the ROC plots, to be shown next, we also have superimposed the operating point of the test, the false positive and true positive fractions for CRC at the threshold used for the test. However, because EXACT FIT is part of the Cologuard algorithm, a threshold does not actually exist for it.

For illustrative purposes, a threshold of 204 ng/mL was chosen, at which EXACT FIT approximately matched the AN specificity of Poly FIT at its threshold.

This figure displays the ROC plots for CRC for the three tests. The circle on each curve denotes the operating point for the test, the false positive and true positive fractions at the threshold used for the test. A global measure of accuracy of the test is the area under the ROC plot, or AUC. Higher values of AUC indicate better discrimination of diseased and non-diseased subjects by the test in a global sense. The maximum value of AUC is 100% and indicates perfect discrimination by the test. For CRC, AUC was 93% for Cologuard and 91.9% for EXACT FIT and 88.0% for Poly FIT.

In this table, the AUCs of the tests for CRC are compared. For the three pairwise comparisons, a positive difference is declared significant if its two-sided 95% confidence interval is > 0 and its two-sided p-value is < .05. No attempt was made to adjust the confidence intervals or p-values for multiple comparisons.

From the second row of the table, the difference in AUC

between EXACT FIT and Poly FIT was 3.9% and is statistically significant with 95% CI > 0 and p-value < .05. Thus, in a global sense, EXACT FIT is a better test than Poly FIT to discriminate CRC from non-CRC.

From the third row, the difference in AUC between Cologuard and Poly FIT was 5.0% and is statistically significant. In a global sense, Cologuard is a better test than Poly FIT.

However, from the fourth row, the difference in AUC between Cologuard and EXACT FIT was 1.1% and is not statistically significant. The 95% confidence interval covers zero and the p-value (.5507) is > .05.

The ROC plot for a test may be used to select a threshold at which to operate the test. The determination of the threshold depends on the tradeoff that is considered acceptable between false positive and false negative diagnostic test errors. At a given operating point, the slope of the tangent line to the ROC plot confers the implicit tradeoff that is being made.

For Poly FIT, the slope of the tangent line at its operating point is shown in red and is rather steep. The seriousness of a false positive error relative to a false negative error is conveyed by this slope. The test operates at a low false positive fraction. A low false positive fraction is a typical operating point for a screening population, because screening involves asymptomatic subjects, the vast majority of whom typically do not have the disease.

In contrast, for Cologuard, the slope of the tangent line at its

operating point is shown in black and is much flatter. Thus, based on the DeeP-C study, the seriousness of a false positive error relative to a false negative error is implied to be smaller for Cologuard at its operating point than for FIT at its operating point. Not surprisingly, Cologuard operates at a higher false positive fraction than FIT, but it also operates at a higher true positive fraction than FIT.

Simply put, Cologuard and FIT are operating at points that attribute a different tradeoff between false positive and false negative errors, even though the screening population is the same. If Cologuard were to operate at the same implied tradeoff as FIT, the slope of the tangent line would be the same and its false positive and true positive fractions could be more similar to those for FIT.

ROC analysis was also used to evaluate Cologuard classification of AN and non-AN subjects. This figure displays the ROC plots for AN for the three tests. Again, the circle on each curve denotes the operating point of the test, the false positive and true positive fractions at the threshold used by the test. For AN, the AUC was 73.3% for Cologuard, 69.3% for EXACT FIT, and 66.7% for Poly FIT.

For all three pairwise comparisons of the tests, the difference in AN AUC is statistically significant. In particular, the difference in AN AUC between Cologuard and EXACT FIT was 4.0% and is statistically significant with a 95% confidence interval > 0 and a p-value of < .05. In a global sense,

for classifying AN, Cologuard is a better test than EXACT FIT, the FIT component, and its algorithm. Moreover, in a global sense, Cologuard is a better test than Poly FIT.

In an attempt to evaluate the benefit/risk of Cologuard for the detection of CRC, Cologuard was compared with FIT on their diagnostic yield in a hypothetical screening population. In this analysis, a hypothetical screening population of 100,000 subjects was considered. The prevalences of CRC, AA, and non-AN were assumed to be the same as those observed in the DeeP-C study among the 10,840 subjects with a valid histopathological result.

The fraction of CRC, AA, and non-AN subjects testing positive by Cologuard and by FIT were assumed to be the same as the fractions observed in the secondary analysis population.

In a population of 100,000 subjects, 700 are expected to have CRC. Among the 700 CRC subjects, the number testing positive is expected to be 647 for Cologuard and 518 for FIT. These are the true positive test results for CRC. Among the remaining 99,300 non-CRC subjects, the number testing positive is expected to be 15,529 for Cologuard and 6,524 for FIT. These are considered false positive test results. The ratio of the number of false positives to true positives in the screening population is therefore 24.0 for Cologuard and 12.6 for FIT.

Taking the difference between the numbers of true positive results for Cologuard and for FIT in the screening population, Cologuard is

expected to detect 129 more CRC subjects than FIT. However, Cologuard is also expected to yield 9,005 more false positive test results than FIT on non-CRC subjects. As the last column indicates, for every extra CRC subject detected by Cologuard, 70 more false positive results are expected on non-CRC subjects.

Safety may also be evaluated in this benefit/risk analysis. A false positive test result on a subject without CRC could lead to an unnecessary referral to colonoscopy. Some of these subjects may experience an adverse event during colonoscopy that would have been avoided had they not been referred. Assuming that the risk of an adverse event during colonoscopy is .68%, Cologuard is expected to yield 61 more adverse events than FIT on non-CRC subjects referred to colonoscopy. Thus, as the last column indicates, for every additional CRC subject detected by Cologuard, the fractional number of additional non-CRC subjects experiencing an adverse event during colonoscopy is expected to be 0.5.

The benefit/risk of Cologuard relative to FIT was similarly evaluated for detection of AN. In a population of 100,000 subjects, 8,280 are expected to have AN. Based on calculations similar to those for the CRC benefit/risk analysis, the ratio of the number of false positives for AN to true positives for AN is 3.2 for Cologuard and 2.0 for FIT. As the last column indicates, Cologuard is expected to detect one more AN subject than FIT at the expense of five more false positive results on non-AN subjects. Regarding

safety, for every extra AN subject detected by Cologuard, 0.4 extra non-AN subjects are expected to experience an adverse event during colonoscopy.

In the clinical protocol, additional analyses were indicated to evaluate Cologuard test performance within subgroups, including subgroups defined by gender, race, and age. Performance goals were not specified for the subgroup analysis. In the subgroup analyses presented now, no attempt was made to adjust for multiple subgroup analyses.

This slide presents subgroup analysis for CRC sensitivity. Cologuard CRC sensitivity varied significantly by gender. The two-sided p-value is .021 and is < .05. CRC sensitivity was 100% for males, 83.9% for females. Variation by race was also significant with a p-value of .012. Among the race groups considered, CRC sensitivity was 96.4% for whites and 62.5% for blacks/African Americans. Variation by age group was not significant in the CRC sensitivity.

For AA sensitivity, variation was not significant by gender, race, or age group. Nonetheless, AA sensitivity tended to increase with age. A statistical test that is designed to detect a trend in a proportion over subgroups is the Cochran-Armitage test. The Cochran-Armitage p-value is .098, which is borderline significant.

For AN specificity, variation was significant by gender, by race, and by age group. In particular, AN specificity decreased with age from 92.2% for subjects less than 60 years old to 77.9% for subjects 80 to 84 years old.

The Sponsor also performed subgroup analyses on subcategories of Category 2, advanced adenoma. For adenoma with carcinoma in situ, high-grade dysplasia, which is Category 2.1, sensitivity was 69.2% for Cologuard and 46.2% for FIT. This analysis was pre-specified in the protocol for the DeeP-C study.

For serrated lesions, Category 2.4, sensitivity was 42.4% for Cologuard and only 5.1% for FIT. This subgroup analysis was not pre-specified in the protocol.

In summary, the primary study goals of CRC sensitivity > 65% and AN specificity > 85% were met using the pre-specified one-sided 95% lower confidence bounds. They were also met with the two-sided 95% confidence intervals.

When the study goals were applied to the complementary pair of performance measures of sensitivity and specificity for CRC, the study goal of 65% for CRC sensitivity was met, but the study goal of 85% when applied to CRC specificity was not. However, after adjustment to the 2010 U.S. census age distribution, the study goals of 65% for CRC sensitivity and 85% for CRC specificity were both met.

In the analysis of the area under the ROC plot for CRC, Cologuard was found to be significantly better than the Polymedco FIT test, but not significantly better than EXACT FIT, the FIT component within the Cologuard algorithm. In a similar analysis of area under the ROC plot for AN,

Cologuard was found to be significantly better than both Polymedco FIT and EXACT FIT.

So this concludes my part of the presentation, and Dr. Abraham Tzou will give the third part of the FDA presentation.

DR. TZOU: Good morning.

My name is Abraham Tzou. I am a medical officer in the Division of Immunology and Hematology Devices.

This portion of the presentation will cover some FDA review considerations relevant to the Panel discussion questions. Selected related background topics will be mentioned accordingly.

Points regarding test performance for Discussion Question 1 will be addressed. The role of demographics will be the topic for Discussion Question 2, along with some comments on screening guidelines. Then proper patient follow-up will be brought up with screening practice and a review of the concept of dwell time for Discussion Question 3. Appropriate scope of claims will pertain to Question 4. Elements of longitudinal study design will be covered for Discussion Question 5.

The pivotal clinical study was designed to examine patients of average risk who would participate in screening by colonoscopy. The Agency suggested to the Sponsor that a cross-sectional clinical study of in vitro diagnostic device (IVD) for colorectal cancer (CRC) screening be designed with a direct head-to-head comparison to a fecal immunochemical test (FIT) assay

with well-documented CRC screening experience in the intended-use setting.

In the pivotal clinical study, Cologuard, CG in the table, had lower specificity compared to FIT: CRC, 84.4% to 93.4%; advanced neoplasia (AN), 86.6% to 94.9%.

And Cologuard had higher sensitivity compared to FIT: CRC, 92.3% to 73.8%; advanced neoplasia (AN), 46.4% to 27.7%; advanced adenoma (AA), 42.4% to 23.8%.

The FIT sensitivity and specificity observed in the pivotal study is comparable to a recent systematic review and meta-analysis that reported point estimates of CRC specificity (94%) and CRC sensitivity (71%) from 12 studies with colonoscopy as the reference.

FDA seeks Panel perspective regarding the acceptability of this tradeoff in sensitivity and specificity. The importance of potential differences in testing frequency for screening program sensitivity will be reviewed later and may be something to keep in mind when comparing cross-sectional performance.

The clinical studies were not designed to assess test performance in subgroups, so those analyses should be interpreted cautiously. Statistically significant differences in device performance were observed based on demographic factors such as age, race and ethnicity, gender. For example, advanced neoplasia specificity decreased with increasing subject age from 92.2% for age less than 60 years to 77.9% for age

80 to 84 years. The pivotal clinical study criteria were for patients 50 to 84 years old.

The Agency seeks Panel input on whether certain aspects related to patient demographics in study design or results merit particular consideration in the product labeling, including materials for patients and physicians. For these discussions, use of the term "patients" is also inclusive for family members or other laypersons involved in caring for patients, while use of the term "physicians" is also inclusive for other healthcare providers and professionals.

Guidelines may be one factor to take into account. There are differences in current CRC screening guidelines in process and content. An example of differences in process occurred when the Institute of Medicine (IOM) established new standards for how guidelines should be developed, and the American Cancer Society (ACS) revised its process for consistency.

An example of differences in content is with respect to age, where the United States Preventive Services Task Force (USPSTF) recommends screening in adults beginning at age 50 years and continuing until age 75 years, recommends against routine screening for colorectal cancer in adults ages 76 to 85 years, and recommends against screening for colorectal cancer in adults older than age 85 years. An upper age limit beyond which colorectal screening is no longer recommended is not specified by the ACS, made prior to its revised process, or the American College of

Gastroenterology (ACG).

Even when there is agreement, screening guidelines are not necessarily followed in clinical practice. Serious deviations from evidence-based recommendations in United States primary care have been reported. For example, instead of diagnostic colonoscopy as follow-up for a positive fecal occult blood test (FOBT) result, physicians recommend repeating the FOBT (17.8%) or using other tests (6.6%).

In light of these deviations from screening recommendations in actual practice, FDA would like to ensure that appropriate materials for each in vitro diagnostic device are provided to patients and physicians.

The clinical performance was evaluated through cross-sectional study. However, test sensitivity from one-time use in a cross-sectional study is distinct from screening program sensitivity achieved through repeated testing assessed in longitudinal study. For example, if two tests have different screening intervals, cross-sectional performance comparison should be interpreted accordingly.

A cross-sectional study at one time point can provide performance for initial use in patients who have not been previously tested using the device and may be sufficient for patients who are positive the first time and should be referred for diagnostic colonoscopy. However, if the device is approved, patients testing negative would not be expected to undergo colonoscopy.

Would repeating device use after a negative result detect significant lesions that were not initially positive? When would follow-up testing occur? A longitudinal study may provide evidence that supports additional repeat testing for patients after initial negative results.

One factor that may affect screening program sensitivity is dwell times. For clinically significant lesions, there may be a range of growth rates, faster and slower. In terms of screening program sensitivity, this would affect how a lower-sensitivity test repeated more frequently compares with a higher-sensitivity test performed less often.

In this graph, disease progression is represented on the vertical axis; time is represented on the horizontal axis. A faster lesion progressing over a short time and a slower lesion progressing over a longer time are depicted.

With less frequent testing, there may be few opportunities to detect the faster-growing lesion. Thus, it is important that evidence of performance adequately supports any claim for less frequent use as part of the colorectal cancer screening program.

With more frequent testing there could be additional opportunities to detect faster- and slower-growing lesions, to the extent that repeat testing is independent; that is, additional testing offers value to identify patients with significant lesions who previously tested negative and subsequently test positive. This may enable a lower-sensitivity test repeated

more frequently to have similar or perhaps better screening program sensitivity than a higher-sensitivity test performed less often. There are randomized trials that are in progress comparing CRC screening with FIT repeated more frequently to colonoscopy performed less often.

In a screening population, there would be a mix of lesions and growth rates with a corresponding spectrum of dwell times. Testing frequency and the distribution of dwell times are the factors for screening program performance.

With this in mind, one of the areas FDA seeks Panel input is appropriate labeling concerning follow-up time interval if a new IVD is approved.

The cross-sectional clinical studies provide performance in patients tested for the first time with the device. While a patient receiving a positive result should be advised to undergo diagnostic colonoscopy, there is uncertainty regarding appropriate follow-up for a patient receiving a negative result.

The frequency based on time interval and the selection of test method for follow-up evaluation can influence screening program sensitivity based on factors such as the degree of test independence and distribution of lesion dwell times. The lack of data regarding repeat device performance in patients previously testing negative may prompt a preference for testing by a different approach that may be more likely to avoid problematic dependent

repeat testing; for example, the lesion does not and will not exhibit alterations detected when repeating the test.

To avoid an excessive time interval elapsing before follow-up screening occurs, it may be prudent for patients and physicians to discuss follow-up screening options and frequencies before testing with a newly approved device, followed by periodic review for those receiving negative results.

FDA seeks Panel input regarding the appropriate scope of product claims. As discussed, there are caveats in extrapolating programmatic performance for CRC screening from cross-sectional data. In the absence of longitudinal performance results from a newly approved device, limiting product claims to first-time use in patients as evaluated in the cross-sectional pivotal clinical study may be an approach to mitigate safety concerns related to cumulative sensitivity and false positive rate with repeated testing. Current CRC screening guidelines recommend that patients undergo routine screening with repeat testing over time.

Thus, longitudinal study conducted to evaluate programmatic performance of the device, in relationship to screening interval, may support long-term safety and effectiveness by providing information such as the negative to positive conversion rate, that is, screening population patients who test negative and then become test positive; the diagnostic yield, that is, clinically significant findings on colonoscopy after a positive test result; and

the predictive values, that is, probability of disease based on a test-positive or test-negative result with repeated use.

The Sponsor has proposed a study to collect longitudinal data on patients prescribed Cologuard over the course of three years. The study schema is depicted here. If subjects test positive by Cologuard at the initial visit, they will be referred for a diagnostic colonoscopy. If subjects test negative by Cologuard, they will have annual follow-up visits in a year and after another year, without additional screening. Patients would then be evaluated at the third year with Cologuard for the second time, and colonoscopy.

Eligibility criteria are designed to select patients who are at average risk for colorectal cancer screening. The primary endpoint for the study is to assess the risk of CRC/advanced adenoma among those with a positive Cologuard test at the third year of follow-up (T3) compared to baseline (T0), with statistical power calculated based on confirming the percentage of patients with CRC/AA at Year 3 is statistically significantly less than at baseline.

It appears that study participants would forego other CRC screening options. Waiting three years to repeat Cologuard testing could be inferior to other approaches. For example, offering annual FIT testing could provide greater safety for study participants. However, depending on how annual FIT testing is incorporated, it could complicate understanding of the

performance of Cologuard at repeat testing when used alone. The appropriateness of the proposed primary endpoint to support repeat testing with Cologuard after three years is unclear.

How does the risk of CRC/AA among those with a positive Cologuard test at the third year of follow-up compared to at baseline relate to performance of other CRC screening options such as annual FIT? What would be the extent of contribution from repeat testing? A device that has limited value for repeat testing, after working the initial time, could have a lower risk of CRC/AA among test positives.

A hypothetical illustration of the proposed primary endpoint with positive predictive value at T3 (PPV3) less than positive predictive value at T0 (PPV0) is provided. At time point T0, pre-test probability or baseline prevalence of disease is depicted on a 0% to 100% scale. The post-test probability based on a positive result equal to positive predictive value zero is depicted in blue. The post-test probability based on a negative result is depicted in dark red.

During the follow-up period from T0 to T3, there would be an incidence of disease among T0 test negatives, leading to a pre-test probability at time point T3. At T3 the pre-test probability could be close to the post-test probability based on a positive result equal to PPV3, depicted in light blue. This suggests that there is limited value of a positive test result at T3, but the proposed primary endpoint could be satisfied even if there is questionable

value from repeat testing at time point T3. The light blue dashed line shows PPV3 < PPV0. Controlling for incident disease cases and selection of meaningful performance criteria to evaluate study results may be considerations for study design.

To understand how screening performance compares to a recommended option such as annual FIT, the percent FIT positive, diagnostic yield from colonoscopy, predictive values, and adherence at T0-T1-T2-T3 would provide a better overall understanding.

In summary, the Panel discussion questions relate to various FDA Cologuard review considerations. For test performance, there is a tradeoff of lower specificity and higher sensitivity in comparison with FIT.

Demographic subgroup considerations relate to study design, differences in guidelines, and observations in performance, including decreased specificity with increasing age.

Issues concerning follow-up arise from taking into account screening practice deviations from guidelines, along with uncertainty regarding testing frequency and lesion dwell times. These also have implications for the appropriate scope of claims.

Aspects of longitudinal study design deal with meaningful evaluation and screening option comparison to address long-term safety and effectiveness for use in colorectal cancer screening programs.

This concludes the FDA presentation. Thank you for your

attention.

DR. PRZYGODZKI: I'd like to thank the FDA presenters today.

We have around 15 minutes for the Panel to ask specific questions to the FDA. Again, as I mentioned earlier, in the afternoon we have the opportunity to speak with both the Sponsor as well as FDA for additional clarification. Fifteen minutes for specific issues that are burning at this point.

Please.

DR. MAHOWALD: I guess this is for Dr. Tzou, just a clarification. What is the rationale for opposing the three-year study versus the annual FIT?

DR. TZOU: I think the general question is to what extent the Panel thinks studying Cologuard performance over the three-year by itself --

DR. MAHOWALD: Yes.

DR. TZOU: -- as proposed in the single arm would be sufficient to appropriately understand that performance?

DR. MAHOWALD: Yes, I guess I'm wondering why -- on what basis is an annual FIT recommended?

DR. TZOU: That is recommended according to guidelines.

DR. MAHOWALD: Generally? Currently?

DR. TZOU: Most guidelines consider annual FIT an appropriate CRC screening option.

DR. MAHOWALD: Okay. So conceivably one could also

recommend the three-year, that that be an annual test.

DR. TZOU: So FDA -- you know, our processes stay separate than what guideline organizations will ultimately say or decide not to say for Cologuard. So the three years, I think, was proposed by the Sponsor as a plausible potential screening interval based on the available evidence, and that's why that was proposed.

DR. MAHOWALD: An improvement because of the interval, I assume.

DR. TZOU: It's based on the relative profile of sensitivity and specificity. I think that it was thought that based on the relative incremental advantage in sensitivity, that less frequent interval might be appropriate.

DR. MAHOWALD: One could conceive, though, of its even being recommended annually --

DR. TZOU: Yes.

DR. MAHOWALD: -- because of its supposed superiority to FIT.

DR. TZOU: The ultimate recommendation for Cologuard will depend on the accumulating evidence over time, as discussed by the Sponsor's presentation, as far as evolution of guidelines over time, based on evidence.

DR. SKATES: This is for Dr. Pennello. This is Steven Skates.

The tradeoff, the safety balance that you derived for Cologuard versus FIT, was essentially justified in my mind by the Sponsor's study choices

of specificity as a tradeoff for sensitivity. And I want to congratulate you on that detail, the quantitative balance between that tradeoff. And that is, I think, the sort of analysis that would be good to do to set the goals in the first place. And I wanted to get your thoughts on that.

And then, secondly, my second question was your increased criterion for a two-sided interval in your test; I would have thought the one-sided would be sufficient. I wanted to push back on why you would even need the two-sided. I thought, in looking for an increase in improvement in sensitivity or specificity, that a one-sided test would be sufficient. So I would like to hear your thoughts on those two issues.

DR. PENNELLO: Okay, thanks for the questions.

The analysis where I was looking at the slopes in an effort to compare the tradeoffs that are being made, which I think is your first question, it was -- no?

DR. SKATES: No, it was the adverse events versus the increased sensitivity --

DR. PENNELLO: Oh, okay.

DR. SKATES: -- that I thought really reassured me on the specificity choice in the end. So in effect --

DR. PENNELLO: This one?

DR. SKATES: Yes, that one. So there was .5 adverse events for each colorectal cancer increase detected.

DR. PENNELLO: Right.

DR. SKATES: And I thought that was a great justification for the tradeoff for specificity choice versus a sensitivity increase. And what I would like to suggest is that sort of analysis be done at the outset as a means for justifying the choice of a specificity or a sensitivity goal, and whether that would have been feasible in this case.

DR. PENNELLO: Well, it may have been feasible. You'll have to ask the Sponsor, but I don't think this kind of analysis was done in order to justify the 65% and 85% study goals. But yes, I would agree, this kind of preplanning of a study might benefit from this kind of configuration.

DR. SKATES: FDA had input into the 85% goal, if I understood the Sponsor's presentation, so I thought maybe something like this might have gone through your considerations in coming up with the 85%.

DR. TZOU: So just as a matter of logistics, this particular study came out after the discussion, some of the discussion. And then some of this data regarding this aspect of it is not necessarily as clear. So this was published in 2012, and this was sort of after the earlier discussion. So would this be incorporated? This is something we could certainly consider incorporating.

The other issue, as far as the adverse event profile, is also appropriately weighting the types of adverse events, because adverse events that are included in this rate are not necessarily all of the same magnitude

either. When you have these sort of composite things, it's certainly helpful to have that overall thing, but then to weight that appropriately also requires more nuance.

DR. SKATES: And then the two-sided/one-sided issue.

DR. PENNELLO: Right.

Well, I think at FDA we like to operate in a sense that whether you're looking at one side of the alternative to the null hypothesis or both, that the same level of evidence should be used in terms of the critical value. And I think, in my mind, you can actually justify that through some decision, statistical decision theory, but I'm not going to get into that.

DR. LIPKIN: Hi. This is Lipkin.

I thank the FDA for a very nice presentation.

I have a question actually about -- I'm not quite sure which of you to address it to -- a policy on kits that are made for home use versus in a doctor's office. So the stool test kind of could go both ways, in a way. I think of patients who are doing this at home. So the FDA obviously has a precedent for approving tests, for example, pregnancy tests, HIV tests. There are home --

Fine. So there is a precedent for home tests, and there are doctor tests in an office, for example, for pregnancy or for detection of HIV. Or I think it's hep C or hep B -- I forgot.

So the question is, what are the different standards? Because

the stool test is kind of -- sort of -- once again in the middle of these two worlds, because I can imagine it being used in rural areas by patients who have access issues. But it also introduces some questions of quality -- you know, quality control, too, versus having it being done in a doctor's office.

DR. GUTIERREZ: So actually we have kind of three levels we look at. We look at prescription use done usually in a laboratory that has good controls. We look at what we call waived testing, which are tests that are typically simple tests done at a physician's office. Those typically are also prescription use. And there are actually -- we have a prescription home use that is like this one, where it's prescribed by a doctor. But part of the test is done at home, and that part could be just a collection part or actually there are tests in which the entire test is done by the user and used at home. And then there's over-the-counter.

In a sense, depending on -- there are issues with all of them, in terms of where the test can go wrong and what needs to be looked at, and they're all different. So it depends a little bit on -- we take into account all the possible pressure points, if you would like, and usually try to have the manufacturers design testing around those points to see what could go wrong and design the test so it doesn't go wrong. But we do take care of all of that when we look at both the testing, the instructions that need to be given, and the level of the language in the instructions. All of that is usually taken into account.

DR. LIPKIN: Thank you.

Then I have a question for Dr. Tzou. I'm pronouncing your name correctly?

Just on the subgroup analyses. You know, this is something that continually comes up; studies aren't powered for this and we get these incidental findings, so to speak. And I'm having a little difficulty -- and perhaps Dr. Skates or Dr. McShane could also chime in -- about how to interpret this issue of looking at subgroups in terms of having CRC, advanced adenomas, advanced neoplasia, and maybe -- you showed us a total analysis; maybe it's right in there -- and this issue of variation by gender and race, which comes up in two of the three categories. And I'm struggling with how statistically robust are those differences, or is there a false discovery rate correction?

DR. TZOU: So I won't give a technical statistical perspective as some of the Panel Members. I will just give sort of a general "review member person" perspective.

So things that come up as part of the consideration, you know, what are the things that were designed to be looked at? What are the things that are important to look at pragmatically? And what are the things that you would have prior to even designing the study or seeing the results, with prior scientific plausibility, right? And it's sort of not always easy to articulate how to put those all together.

So for aspects that -- for cancer detection rate, for advanced adenoma detection rate, for other category detection rates that were relatively clearly specified, those probably are more important to consider whether that performance is appropriate. For other clinicopathological categories where one would be interested in, those are some things -- you know, although they may not be robustly powered in the study design, those are something we always look at just to see what is the consistency of the performance.

If there are some of those clinical covariates where one would have a suspicion based on the existing literature or prior knowledge that there are differences in methylation status, as I think you suggested earlier, there might be a particular tendency to suspect that to begin with. Then that perhaps lends more credence to certain findings that might lean in a certain direction.

DR. LIPKIN: Let me just rephrase my question a little bit. And this may be in here, but I can't locate it.

So I understand that there is this issue of variation by gender and race that I see for these three categories. Was that done for all of those three categories together, in terms of looking at whether there's variation for CRC plus AN? Is that in the packet?

DR. TZOU: I don't think we provided the combined interactions, but --

DR. PENNELLO: No, we didn't do that analysis where we looked at finer subsets.

DR. SKATES: Or putting all three factors into the model at one time and seeing if sensitivity --

DR. PENNELLO: Yes.

DR. SKATES: -- jointly was affected by any of these three factors?

DR. LIPKIN: Or some sort of like a sensitivity --

DR. PENNELLO: Right.

DR. LIPKIN: Yes, a sensitivity type of --

DR. SKATES: Well, there's the sensitivity. But then a multivariate prediction model could have been another way to deal with that in one go.

DR. PENNELLO: We did do some logistic analysis of the odds ratio, but we didn't separate the CRCs versus the non-CRCs and do a logistic on that with age and gender as predictors. We didn't do that.

DR. WECK: So in the Executive Summary, the race or ethnicity data are broken down by CRC versus advanced adenoma. But the numbers are so small, they're not likely to be statistically significant, I would think. And so the question is, is the verbiage in the insert that says that the sensitivity for advanced adenoma is higher in American Indians than Alaskan natives, there may not be sufficient data to state that? That would be my one

caveat.

But they were looked at individually by CRC and by advanced adenoma, and I think it needs to be looked at carefully, whether those are statistically significant and how that should be included or not in the label.

DR. LIPKIN: Lipkin. Just very briefly.

So one of the things I was kind of thinking of here -- which I think was alluded to in the first part of the presentation -- the different pathways to colorectal cancer mutagenesis. And one way, at least, of dividing this roughly is sort of the pathway that bifurcates with the serrated adenoma pathway and then the logistics -- the regular or wind-driven, or whatever -- KRAS related and bleeding related.

So in the serrated adenomas, for example, there is a different -- for instance, there are higher rates in women. And that's why I'm just sort of struggling here, to think about whether this is the totality of the data or it's something that may reflect these differences along these two pathways. And the methylated markers basically -- perhaps one interpretation is that they are largely picking up the patients from the serrated adenoma kind of pathway.

DR. PRZYGODZKI: It almost seems to some extent that the advanced neoplasia category itself is really what we're homing in on, regardless of what histological subset -- because the histological subset will come through the pathology itself. The thing is to find that neoplasia at that

point.

One more question and we need to break.

Please.

DR. SKATES: So this is, I think, a question for the FDA.

But the Sponsor says that the results will be provided as a black and white positive or negative, but it's based on multiple measurements that are continuous in subgroups of those that could be reported, like KRAS mutations and methylations and hemoglobin level and the composite score.

I would like to understand, from an FDA perspective, whether there's more information to the doctor or it would be better to have the doctor more informed by having those levels presented in the report, as well as the plus-and-minus of the ultimate score. And I mentioned 183 is the cutoff, meaning 18.3% chance of having colorectal cancer, or something like that. So having more information, I would have thought, for the physician or the healthcare provider, would be a better way to report the result.

DR. TZOU: Thank you for the question.

I think, Dr. Skates, you've had some familiarity with products where there are these complex scores and algorithms that may be considered for FDA consideration. So this is not the first time FDA has considered this issue. It's not the first product where this kind of thing comes up.

So at the first level there are qualitative results. There could be -- you provide the score, in addition. You could potentially provide a lot of

the components of the score, in addition. So I guess the general framework, I would say, for that is -- you know, this is all increasing levels of granularity of information provided. One general question is, is there additional value from that additional granularity?

So if you say, I start off with plus/minus and I give you a number, a higher or lower number, then does the higher or lower number translate to something that is clinically associated with something that's different? And if you say, I want to give you all the components, too, does that also translate into something meaningful?

So I guess those could be entertained. I guess it's really the level to which one would be able to support that there really is additional information gleaned from going that far.

I think in the context of -- you know, one of the things I discussed was screening practice deviations. In the primary care setting, even with something as well established as FOBT and just having plus or minus, the clinical outcome may not be as optimal even with something as simple as that. And for us to say well, we have something that's new, it has all of these markers and provides all of this information and gives all of this out there --

DR. SKATES: I mentioned that KRAS mutation status would be helpful for the treating medical oncologist. This is an area I don't know much about, but I could imagine that information downstream being helpful.

DR. TZOU: Sure. So KRAS mutation status -- you know, this is a

little far off the particular thing. As far as how prevalent that is in the population and what exactly that means by itself, it's probably -- there are a lot more issues to discuss. So in principle that's something, but really the evidence to support that might be more contextualized and require greater discussion.

DR. PRZYGODZKI: Okay, one final one because we have to get going.

DR. McSHANE: Okay, just to follow up on that.

Since I live mostly in the cancer treatment world, I would imagine you'd quickly get into issues like well, okay, there's KRAS mutation, but in what exon is it? And you may have devised this test a particular way, which doesn't necessarily mean that it gives me all of the information I need for treatment. So I think I'm guessing that that's the concern you have --

DR. TZOU: Sure.

DR. McSHANE: -- that it wouldn't be validated for the use that it might be put to --

DR. TZOU: Sure, right. Sure.

DR. McSHANE: -- if you report it in the report.

DR. TZOU: Right. In a treatment setting of a patient who has been diagnosed with cancer -- and where in the GI tract is this emanating from? Does it correlate to what you're actually interested in? It is much more complex. In the general population, screening population, then the

prevalence even of colorectal cancer is quite low to begin with. So it's not a diagnosed cancer population where treatment is being considered. Of course, those are quite different issues.

DR. SKATES: I guess I come from the CA 125 world where you report the CA 125 and not just when it's above 35 or below 35, and then the doctor takes it from there.

DR. TZOU: Sure. In the CA 125, at least we're monitoring claims. We also look at how the values change over time and whether a clinically significant change correlates to disease progression and clinical status over time. So that's a different design, also.

DR. SKATES: Okay, my gut sense is that it would be more helpful to accumulate evidence over time, if the physician had that report that was more detailed.

DR. PRZYGODZKI: Well, we'll have much more ability to discuss about these questions and others after lunch. We will break until 12:30.

I request the Panel not to speak with the public at this point. I also would like to note that the room will be closed. Please take your possessions as you leave.

Thank you.

(Whereupon, at 11:35 a.m. a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:30 p.m.)

DR. PRZYGODZKI: I'd like to ask for everybody to grab a seat.

Okay. So right now is when we have the public speaking portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

Ms. Waterhouse will now read the Open Public Hearing disclosure process statement.

MS. WATERHOUSE: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationships that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such

financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. PRZYGODZKI: Okay. So we have six folks that want to speak. Each person will have five minutes. I'd like to ask for you to please speak clearly into the microphone and note who you are so the transcriptionist can take your name down and information.

The first person is Kim Ryan.

MS. RYAN: Nice to see you all again. My name is Kim Ryan.

I am Director of Patient Information Services for an organization by the name of Fight Colorectal Cancer. Fight Colorectal Cancer is a nonprofit and nonpartisan advocacy organization based here in Washington, D.C. that is committed to the fight against both colon and rectal cancer.

Fight Colorectal Cancer fully believes in disclosing all conflicts of interest. We have received unrestricted funding from companies such as Fuji, Given Imaging, Quest Diagnostics, Exact Sciences, and Epigenomics. None of these companies nor our other corporate supporters have influenced our comments on this issue.

So rather than repeat some of the screening statistics that I talked to you guys yesterday about, I'm just going to cut to the chase regarding a very popular phrase that we've heard over the past two days, and

that is that the best screening test is the one that gets used. And we really need good screening tests.

We also need tests that address strategies to barriers to compliance for patients, particularly among the 23 million Americans who should be screened but have not been screened. For example, some screening programs rely on access to appropriate care. Rural or underserved patients may not have access to screening colonoscopy. However, they may have access to a stool-based test.

Screening programs also need to take into account patient preference. For example, patients may have comorbidities which would increase the risk for the prep and sedation for a standard colonoscopy.

And, lastly, people without symptoms may simply refuse to have an invasive procedure such as a colonoscopy and the prep required. However, they may be willing to proceed with a less invasive procedure such as a stool-based test.

In all of these scenarios, if the initial test is positive, the patient and provider would have a significant incentive to schedule a diagnostic colonoscopy.

So, ultimately, sensitivity and specificity data are what matter most, along with the interval of testing. And we are listening with great interest as you consider these issues today.

If a novel test could improve compliance in a noncompliant

population, we wonder if you might consider whether a limited indication might help increase compliance in a very targeted way. In that vein, perhaps it's possible to target populations who refuse or don't have access to standard interventions with the novel test that you're considering today.

In all situations, we urge you to look at the planned postmarketing research. Ultimately, we would like to see sponsors and payers work together to create a healthcare learning system which generates robust data that will help increase compliance in a way that decreases incidence and mortality.

While we realize that the FDA and this Panel cannot require such studies, we urge you to think big to ensure that this new test has the impact that we're all looking for, which is fewer deaths to colorectal cancer.

On behalf of Fight Colorectal Cancer, we'd like to thank you for your time and for your careful consideration of these issues.

DR. PRZYGODZKI: Ms. Ryan, thank you.

The next person is Dr. David Ransohoff.

DR. RANSOHOFF: Thank you.

I will discuss noninvasive tests in colon cancer screening and address, first, is colonoscopy the best test? Second, the need to consider programs of screening using noninvasive tests because programs of noninvasive testing, over time, may be better than a program of colonoscopy.

My career has focused on screening, including a process to

evaluate diagnostic tests, evaluation of cancer screening tests -- including those listed here -- screening policy, and the process to make guidelines more trustworthy.

My conflicts or relationships include the Sponsor, for Exact, as a paid consultant until 2002. Since 2002 no financial interest. For Epigenomics, no financial interest. For FDA, I am a member of a devices panel. Today I speak for neither sponsor. My reason to speak is to address FDA's concerns regarding guidelines and recommendations about noninvasive tests.

FDA said, in the *Federal Register*, it wants a test to be used in accordance with recognized screening guidelines but then noted in the Executive Summary that recommendations differ. Some say colonoscopy is preferred. So is colonoscopy preferred, the gold standard, best? And what is the role of indirect tests? My comments concern how do guidelines differ, why and which to trust, and what is the role of indirect tests and how do we assess that.

The major screening guidelines differ, as the FDA noted in what they say. The American Cancer Society Multi-Society Task Force -- this is multi-GI societies -- and the American College of Radiology endorse indirect methods like fecal occult blood testing, but also state "a structural exam is preferred," interpreted as colonoscopy is preferred.

In contrast, the U.S. Preventive Services Task Force concludes that any of several programs, including occult blood testing, is acceptable.

This phrase "structural exam is preferred" received intense attention of doctors in gastroenterology and primary care, interpreted as colonoscopy is preferred.

Why the difference? The answer is process, the process to make guidelines differ. For the ACS Multi-Society Task Force, there were no pre-stated rules of evidence, no assessment of outcomes, benefit and harm, quantitatively. Conflict of interest was not managed. The process involving mainly gastroenterologists and radiologists -- no generalists and methodologists -- was described as political, in print, by a panelist. The U.S. Preventive Services Task Force handled each process better. That is why the S's are there.

The U.S. Preventive Services Task Force, in assessing evidence, uses a quantitative analytic framework resembling a clinical trial. I know you can't read this, but the tests are done here, indirect tests are done here, outcomes are measured here, and there are lots of steps that happen in between, as if you were doing a trial.

These differences in process between the two sets of guidelines were noted in the Institute of Medicine's C*linical Practice Guidelines We Can Trust* report as a case study, and the box over here comparing the two guidelines to illustrate deficiencies in the ACS Multi-Society Task Force that had said colonoscopy preferred. That guideline was less trustworthy. Indeed, these events prompted the American Cancer Society to devise and describe in

this article in *JAMA* an entirely new guidelines-making process evolved from the old. These events illustrate, then, in the field of guidelines -- that FDA and others will consider -- not all guidelines are created equal. That's one thing that this example illustrates.

Last -- and that's also illustrated by the examples -- how can colonoscopy not be best? And the Preventive Services Task Force's quantitative analysis shows how. At any one application, colonoscopy is best because it's very sensitive and can remove lesions. But in a program of screening, colonoscopy every 10 years, for example, may miss new or rapidly growing lesions that may be detected by less sensitive noninvasive tests done more frequently.

And this means that we need to consider program sensitivity and specificity as well as application sensitivity and specificity. And program sensitivity and specificity depends, as we heard Dr. Tzou start to describe this morning, on issues like test independence. It's related to biology, dwell times -- whether over time lesions bleed, have mutations, and so forth, the questions not addressed in one-point-of-time studies.

In conclusion, then, guidelines do differ. The "colonoscopy best" guidelines are not as trustworthy as the U.S. Preventive Services Task Force. Programs of noninvasive tests are historically supported by the task force, and as tests may improve, such tests may continue to have an important role. The bottom line is we need to understand and consider

program performance as well as application.

Thank you.

DR. PRZYGODZKI: Thank you, Dr. Ransohoff.

The next individual is Dr. Whitney F. Jones.

DR. JONES: Good afternoon. My name is Dr. Whitney Jones.

I am a practicing gastroenterologist and a clinical professor at the University of Louisville, and the founder of two organizations in the state of Kentucky: the Colon Cancer Prevention Project and the Kentucky Cancer Foundation, who seek to improve awareness of and access to screening tests for both the insured and the uninsured.

I am being reimbursed for my travel today, but otherwise I have no financial involvement with Exact Sciences, and I'm not an equity shareholder.

Thank you very much for this opportunity today on this very important hearing regarding FDA approval of the Cologuard screening system. And I would like to also thank the people in the audience, for the work of the Panel, the FDA, CMS, the staff, and industry, who are playing important roles toward the collective goal of preventing and reducing the burden of colon cancer on our society, and by working toward our collective goal of screening 80% of our population by 2018.

Through the foundations and our partnership in the state of Kentucky, we have dedicated ourselves to reducing unnecessary suffering and

premature deaths from colon cancer. And as the nation's leading state for incidence in colorectal cancer, I can say that screening makes a difference.

Our partners on the ground are from boots, folks who are out there in communities, screening folks and talking to folks -- all the way up to our governor, Steve Beshear, who has allotted $1 million every two years to help screen the indigent, himself a cancer survivor. Our private-public partnership model to fund cancer screening for the uninsured serves as a model and today, in Kentucky, screens uninsured people across the spectrum.

A decade ago we led the nation in colon cancer cases and colon cancer deaths. We were 49th in screening rates -- what a shocker. Today, our screening rate has doubled; we are at the national average. Our incidence and mortality are both down 22%, respectively, and early stage cancer cases now outnumber advanced colon cancer stages in our registry for the first time ever, a testament to the benefit of screening.

So for the nation's cancer-leading mortality state, we have made great progress. But the job is not done. Improved noninvasive testing is a key toward our goal of making colorectal cancer, like cervical cancer -- for the most part -- a disease of the past.

My testimony and support for the approval of Cologuard is based on the answer to the following questions, which I ask every day of myself as I serve my patients:

Will Cologuard help us, in the colon cancer prevention

community, better serve the patients at risk in our population that we serve? My opinion, based on the available information, is an unequivocal yes, with three major points to support that observation.

First, the DeeP-C study unequivocally proves that Cologuard is significantly superior over the current standard stool-based FIT testing for colorectal cancer. This single finding alone warrants approval. It is, in fact, a better mousetrap, if we're focused on minimally invasive testing.

Second -- and equally, if not more important -- unlike FIT testing, Cologuard, by design, picks up advanced adenomas, including up to 7 and 10 adenomas with high-grade dysplasia. To be clear, these are what your doctor is looking for when he or she does your colonoscopy. And the fact that we can narrow the field of these and better utilize colonoscopy is a huge advance forward. Also serrated adenomas -- a real puzzle for us up until the last 10 years -- are addressed by this new screening technology.

FIT testing is not designed to detect polyps; Cologuard is and, so for the first time in noninvasive tests, orders a preventative component to testing. To be clear, remember that colonoscopy did not significantly reduce colorectal cancer incidence until we started removing adenomas. So the fact that our incidence and mortality rates are down is a testimony to the importance of identifying and removing these pre-cancerous lesions.

Finally, the reality in colon cancer screening is that many people we seek to serve -- including but not certainly limited to disparate

populations such as African Americans, Hispanics, rural populations -- particularly Appalachia -- do not want or cannot get colonoscopy. I should know. I spend my days talking people into getting one all the time, or an alternative screen. Some people just don't want to have it. No matter how many times their physicians ask them, they are going to say no. But with increasing frequency, they are saying yes to noninvasive stool testings that don't require major changes in diet, with a user-friendly collection process such as FIT. In fact, FIT is our state-preferred screening program for our uninsured population, along with colonoscopy.

Myself, my patients -- and, I suspect, you and your families also favor prevention to early detection alone. Through Cologuard's approval, the non-colonoscopy population, in addition to better colorectal cancer detection, can finally participate in both early detection and prevention to high-risk adenoma.

So, in summary, I strongly support the approval of the Cologuard system and its transformational potential to accelerate advanced reductions in the burden of colorectal cancer in our country. Cologuard approval will be welcomed in the colorectal cancer --

DR. PRZYGODZKI: Excuse me. Complete your remarks, please, because we need to move.

DR. JONES: -- community.

Thank you very much.

DR. PRZYGODZKI: Thank you. Thank you, Dr. Jones.

The next person is Eric Hargis.

MR. HARGIS: Hi, good afternoon.

I would first like to thank the FDA, CMS, and members of the Advisory Committee for the opportunity to provide comments this afternoon. My name is Eric Hargis and I serve as the chief executive officer of the Colon Cancer Alliance, the largest nonprofit patient advocacy organization dedicated to the prevention of colorectal cancer and empowerment of patients facing the challenge of this devastating condition.

In the past decade we've seen a 30% reduction in the incidence of colorectal cancer, a dramatic decline for any medical condition, but even more astounding given our aging population and the fact that colorectal cancer primarily impacts older adults. The reason for the decline is clear. An increase in the percentage of at-risk adults who are screened resulted in a corresponding decrease in colorectal cancer.

But despite this improvement, 23 million Americans in the at-risk group for colorectal cancer have not been screened at all. This year there will be an estimated 140,000 cases of colorectal cancer, and the treatment of these individuals will cost in excess of $14 billion. It is truly an American tragedy that in 2014 almost 50,000 people will die from a condition that is largely preventable with timely screening.

We believe the best method of screening to prevent colorectal

cancer is a colonoscopy, in that it is the best way to identify pre-cancerous polyps and remove them in the same procedure. But we will not reach the goal of screening all at-risk adults if we rely solely on the colonoscopy. There are a host of factors that prevent or inhibit individuals from getting a colonoscopy, from lack of insurance, to embarrassment, to stigma. But perhaps the highest hurdle is simply the fact that it requires someone who has no symptoms, in fact feels healthy, to undergo a fairly invasive medical procedure. The fact is, we need new less-invasive screening methods if we are to reach the nationwide goal set by the roundtable, of screening 80% of at-risk adults by 2018.

That is why the Colon Cancer Alliance strongly encourages the FDA to approve Cologuard as a new screening option for physicians and their patients, and that CMS include Cologuard for reimbursement to ensure that a test that could save millions in treatment costs and, more importantly, patients' lives is not avoided due to cost.

Certainly, the Colon Cancer Alliance recognizes that Cologuard cannot detect pre-cancerous polyps as well as a colonoscopy, but we stand with Dr. Koh, Assistant Secretary of Health and Human Services, when he says the best screening method is the one that gets used. There is a huge need for more effective noninvasive tests, and we look forward to a speedy and positive decision by the FDA and CMS.

Thank you again for the opportunity to provide comments.

DR. PRZYGODZKI: Thank you, Mr. Hargis.

Jasmine Greenamyer.

UNIDENTIFIED SPEAKER: She's not here.

DR. PRZYGODZKI: Not here, okay. Then the next individual is Marcia Mullins.

MS. MULLINS: Thank you for allowing me to speak to you today. I am honored to be here.

I would like to disclose that my travel expenses were paid for by Exact Sciences.

My name is Marcia Mullins. I am from Huntington, West Virginia, the land of *We Are Marshall*. I am a Stage IIIC rectal cancer survivor, and I am currently in remission. I was 58 years old when I had a rectal hemorrhage and was admitted to the hospital to have a colonoscopy the next morning. I am now 60 years old. I should have been screened when I was 50 years old, but I did not want to have a colonoscopy. I did consider using an at-home screening test, but since I had bleeding hemorrhoids, I thought that that would make an at-home test that looked for blood inconclusive.

To find out if I was at risk, I studied the colorectal cancer risk factors list and breathed a sigh of relief. I did all the right things in my lifestyle and diet, except for being moderately overweight. Plus, colorectal cancer did not run in my family. I thought I was free and clear -- I was wrong. I wish there was no risk factor list. I wish instead there was this statement:

Colorectal cancer is the largest cancer killer of nonsmoking Americans. If you have symptoms of colorectal cancer, or if colorectal cancer runs in your family, or if you are 50 years old or older, you are at risk. Get screened. Period.

Eating well, taking vitamins, no drinking, no smoking, et cetera, are all really moot when it comes to being screened for colorectal cancer. I almost died because I pinned my hopes to the risk factors list when my real danger was what I call the polyp factor. I did not know that colon polyps often develop as we age, and that colon polyps can become cancerous. I was also unaware of the early warning signs of colorectal cancer, which are -- oh, wait. There are no early warning signs of colorectal cancer. By the time there are symptoms, it's usually advanced.

After my diagnosis I was very blessed. My insurance company sent me to Memorial Sloan Kettering for a second opinion. There I became part of an in-house study that is now a national trial. It was called neoadjuvant FOLFOX for non-metastatic, locally advanced rectal cancer.

The treatment was arduous, but it worked very well for me. After an eight-hour surgery, I have a rearranged plumbing system and a permanent ostomy that I have nicknamed "Brat." And I have my life. I'm being carefully monitored. When I asked my medical oncologist how long he would be watching me, he said, "For the rest of your life."

But all of this, the life-threatening danger of this cancer, the

fear, the pain, the incredible expense of treatment and surgery, the impact it had on my family, all of this could have been avoided if I'd only gotten screened on time.

I am now a full-time volunteer colorectal cancer awareness advocate. I share my story, and I give people the facts about this preventable killer. But awareness will not change the fact that many people are disinclined to have a screening colonoscopy or to use a fecal blood test.

My three adult children are at risk for colon cancer because of my diagnosis. None of them want to use a fecal blood test. My sons both refuse to have a screening colonoscopy. My daughter is not opposed to having a screening colonoscopy, but she is a very busy wife and mother. She has a full-time job as a paralegal in a law office and is working on getting her master's degree. A colonoscopy would take two and one-half days out of her schedule; the pre-surgical testing and then the prep and then the procedure itself. She just doesn't have the time right now.

A first-line dependable screening test that's easy to use, painless, requires no preparation or dietary or medication restrictions, and that needs only one sample would be a game changer in the battle against the largest cancer killer of nonsmoking Americans. I believe Cologuard can be that game changer.

By the way, I've taken an informal study -- survey, sorry. I've taken an informal survey of my friends and my family members who haven't

been screened, like me, and they think that a stool DNA test that's designed to identify recognizable DNA changes in cells that are shed from the lining of the colon through stool is really cool and they would definitely use it. And I would have used it, too.

Thank you.

DR. PRZYGODZKI: Thank you, Ms. Mullins. Thank you for sharing your experience. And we on the Panel wish you all the best along and to a free life.

With this I'd like to open the -- if there are any questions from the audience for the Panel. If there are, please step up, identify yourselves and we'll give you three minutes of time.

(No response.)

DR. PRZYGODZKI: Having seen nobody moving, I would like to ask the Panel, are there any questions for the audience participants that presented?

Yes, you have a question?

No, okay.

DR. NOSTRANT: I guess I have one question. As Dr. Skates talked about, was there any information as regards to the absolute value of the test in either determining location of cancer or size of cancer or any of those types of efforts being done? Because that's going to be important to the gastroenterologist, who now is going to be doing many more

colonoscopies for which the predictive value of cancer is going to be present, and we don't want to miss any of those. So I was just wondering if there was any more information on that.

DR. PRZYGODZKI: Right now we will -- I still want the audience to answer that at this point.

I'm sorry, I just want to keep this nice and clear and clean. It's procedure. Thank you.

Okay, at this point I officially close the open meeting.

Now we'll go to the Panel deliberation. Now we're going to be able to talk about all of these things.

Although the public is certainly present, we ask that if you do have a burning question, to again ask me, if there's a need to do that.

Are the Sponsors ready for additional questions?

(No audible response.)

DR. PRZYGODZKI: Great. How about FDA?

(No audible response.)

DR. PRZYGODZKI: Great. So right now I would like to ask the Panel to ask either the Sponsor or FDA questions, as need be.

You started off, go right ahead.

DR. NOSTRANT: I'd like to ask the Sponsor that question I just gave.

(Laughter.)

DR. LIDGARD: Thank you, Dr. Nostrant.

Graham Lidgard, Exact Sciences.

Within the Cologuard results, we report just a positive/negative. We don't provide any other information within the test, and I don't think there would be any information that would help you determine location of any of the lesions.

DR. NOSTRANT: Was any information actually tried to be obtained or in retrospect obtained? I know you didn't do it. And positive/negative was very appropriate. I'm not saying that.

But was there any information that would be given to the practicing gastroenterologist who's going to act upon this test as the primary agent to determine these things?

And I can tell you, if I have a pre-test probability that there's a high potential for cancer present, or a higher potential, I'm going to spend a lot more time looking very, very closely at that patient group. So I was wondering if I can get more information. Or is any information more appropriate?

DR. LIDGARD: We haven't analyzed the actual results to be able to look at location or even size in the data.

DR. NOSTRANT: Thank you.

DR. PRZYGODZKI: Ms. DeLuca.

DR. WECK: This is Karen Weck.

But I think, from reviewing the data, there were data to indicate that both proximal and distal lesions are picked up by this assay with about equal sensitivity. So I think you would have an equal indication that there was a chance for a colorectal cancer, but there was nothing that differentiated the two types of lesions. And then there were also indications that although the sensitivity is highest for colorectal cancer -- you know, of about 91% -- that there is also the ability to pick up advanced adenomas and even smaller lesions, but with decreased sensitivity.

But nothing about the score. That wasn't presented. There wasn't any data that -- anything about the score, itself -- could tell you any more about the size of the lesion or the place of the lesion.

DR. NOSTRANT: No, they didn't present that because they're only determining positive or negative. But they did show that if left-sided lesions appear to have a stronger association with a positive test, then right-sided lesions -- and that's why I wanted to find out --

DR. WECK: I see.

DR. NOSTRANT: -- was there anything to determine the size. That's all I was asking.

DR. PRZYGODZKI: Ms. DeLuca.

MS. DeLUCA: Jo-Ellen DeLuca.

I have a question concerning labeling. My trade or my career was as a reading specialist, and I find, even when I go to the doctors' offices,

sometimes they ask me what this means, that label. Patients have a very difficult time, and if this is something that a patient may see -- or somebody who's not even a patient yet -- worse still, rural area -- worse still, has a less than third grade education, often the case in my area of the country -- like Dr. Whitney Jones, how clear are the directions on the label? Will people be able to understand them? Are they too long, too syllabic? Are they simple enough for people to follow? How scientific are you getting, I guess, would be the bottom line for the patient.

MS. STATZ: Sandra Statz, Exact Sciences.

We have developed a patient guide that is included within the collection kit that was written for a seventh grade level, and it was tested in human factors testing with individuals with lower levels of reading, as well.

MS. DeLUCA: And size of font?

MS. STATZ: I don't remember the size of the font.

MS. DeLUCA: Those are two very important things. A seventh grade level for many people is a college education. Sorry.

MS. STATZ: I can check and see what the size of the font was. There were also pictures included. And, again, we did test in populations that had lower-level reading.

MS. DeLUCA: Thank you.

DR. GATES: I just had a question on interpretation. I just want to make sure I was interpreting one of the figures right. For the FDA it is -- I

think -- Slide 64. It's the ROC figure. And I'm looking at it.

DR. PRZYGODZKI: Can we have that slide up, please?

DR. GATES: And I want to just make sure I was interpreting it right or whether I was reading it right. But at any rate, Cologuard has an AUC of 93 and EXACT FIT an AUC of about 92. Cologuard is made up of three different components, one of which is EXACT FIT and the other one is the methylation and the other one is the KRAS.

Would that mean that the EXACT FIT contributes about 92% of the discrimination and the other two tests only add a couple more percent for CRC? Is that the way you would interpret that?

DR. PENNELLO: Right. So the algorithm included EXACT FIT, the Cologuard algorithm, as one component, and then there are the DNA markers and --

DR. GATES: Right. And they all go together into one Cologuard --

DR. PENNELLO: Into the Cologuard composite score between 0 and 1,000.

DR. GATES: But if you dissect out the EXACT FIT, that contributes about 92. And then the whole kit, Cologuard contributes another couple of percent.

DR. PENNELLO: Right, right. In terms of area under the ROC curve.

DR. GATES: Right.

DR. PENNELLO: Which is a global assessment.

DR. GATES: Right. So that would say that most of the discrimination is coming from the EXACT FIT component. Is that a fair assessment?

DR. PENNELLO: Well, it's a little bit hard to interpret the area under the ROC curve that way because it's varying the threshold over all of the values of the test that were observed as opposed to the binary 1 of positive or negative at the threshold used, which is 183. And maybe to provide further interpretation, the area under the curve for a random test would be 50% expected.

DR. GATES: Okay. Well, that's about the same. Okay.

DR. ITZKOWITZ: If I may add to that? Dr. Itzkowitz.

The way this analysis was done was by removing the hemoglobin component of the EXACT assay and analyzing that metric separately. In fact, the Cologuard assay itself has an algorithm where that is not pulled out individually. So it's a little bit difficult to know -- we call it the EXACT FIT test, but it's really just the hemoglobin component of the whole assay.

And I think ROC curves and area under the curve give us some idea of performance. But we have to realize that in the clinically relevant range, where we are usually looking for a diagnostic test -- say like 85% to

90% specificity -- that incremental benefit of the whole Cologuard test is much better than either the EXACT FIT test or the Polymedco FIT test.

DR. PRZYGODZKI: Dr. Weck.

DR. WECK: Yes, I wanted to ask a question to either the Sponsor or the FDA about the cross-reactivity studies, which weren't presented to us here. But I just wanted to state that this is exactly what I would want to see out of a screening test, which is that there is very high sensitivity. And the ROC curves are kind of a measure of both sensitivity and specificity.

So to me, sensitivity is the key factor here, where the sensitivity for colorectal cancer was 91% to 92% and performed better than the FIT test. And the sensitivity even for advanced adenomas was much higher via this test than the FIT test -- so 42% versus 24%, which is ideal for a screening assay.

And then the hit to specificity. You know, I'm willing to have to have a false positive in 15 out of 100 people with this test versus 5 out of 100 with the FIT test in order to gain that sensitivity. And I think it's also intriguing that even in the negative samples, there was an indication that this Cologuard test is perhaps picking up earlier lesions. So some of the false positive results could be due to either less advanced adenomas or early non-neoplastic lesions. So there's a potential that you may be picking up even earlier lesions which then, when followed up with colonoscopy, could be potentially curative.

So in terms of the specificity data, I think that the studies were done properly in terms of the samples that were analyzed for specificity, which were no evidence of disease by colonoscopy or very early or small adenomatous lesions by colonoscopy. That's the right controls, I think. But cross-reactivity studies were also done, which is what I wanted to discuss.

So I noted that there was some cross-reactivity with other types of cancer and with inflammatory bowel disease of between 36% to 50%, including gynecologic cancers such as ovarian and cervical cancer; 36% positive; hepatic cancer, 50%; pancreatic cancer, 41%; and inflammatory bowel disease, 39%.

So although the numbers were small, there were a significant number of specimens tested, and I just wanted to discuss, you know, what does that mean for this test? If we have a positive test and colonoscopy is negative, does that mean we should screen for additional GI cancers? Probably the answer is no, not right now. That needs to be studied in a clinical study. But is this something that should be included in the package insert, that there may be a false positive result due to other cancers?

And, in particular, for patients with inflammatory bowel disease who may have a false positive rate of 39%, does that mean that this test is not indicated for that population? Or if the test is indicated for that population, does that mean there should just be a comment that there may be a false positive result?

DR. AHLQUIST: Thank you.

Dave Ahlquist, Mayo Clinic.

An important question. And I think it's important also to emphasize that these were symptomatic patients with pancreatic cancer, with hepatomas, with ovarian or uterine cancers, and we would not be -- they would not qualify for a routine colon cancer screen. But they were patients that we could study because they had known diagnoses.

Furthermore, in an earlier protocol with an earlier iteration of the stool DNA testing, we actually formally did do very extensive upper GI testing in patients that were test positive/colonoscopy negative. And after nearly 100 consecutive of such instances where the upper GI studies were entirely negative, our IRB discontinued those studies because of the low yield. And, statistically, there would be a miniscule chance of finding an asymptomatic lesion with a test designed to focus on colon lesions.

DR. WECK: Thanks for that clarification.

And regarding inflammatory bowel disease?

DR. AHLQUIST: Yes. And inflammatory bowel disease, excuse me. Those are symptomatic patients, and they would be excluded as an indication for using this test.

DR. PRZYGODZKI: Dr. Lipkin and then Dr. Bujold.

DR. LIPKIN: Lipkin.

Can the Sponsor articulate what is the difference between the

Poly FIT test and the EXACT FIT test? Because they're statistically significant in their abilities to pick up colorectal cancer.

DR. LIDGARD: There are two major differences. One is the methodology. The Polymedco FIT is an immuno-aggregation method, so it uses light scattering to measure the immune complex and it has lower sensitivity for hemoglobin. But it also uses smaller sample sizes. A second difference is a smaller sample size. It uses 10 mg of stool, and we use 20 mg of stool.

DR. LIPKIN: Thank you.

So that's something that was developed -- EXACT FIT, I mean, it's something that was developed by your group, right?

DR. LIDGARD: Yes, that was developed by the Exact Sciences team.

DR. LIPKIN: Okay.

DR. PRZYGODZKI: Dr. Bujold.

DR. BUJOLD: Ed Bujold.

This is two questions for the Sponsors. And this is kind of a follow-on to Jo-Ellen's question.

You know, we've been told that patient education material that we give to patients, or instructions we give to patients, should be at a third to fifth grade reading level at this point. And I noticed in the study that there were several of the samples that were excluded -- it didn't actually explain

why they were excluded. But I wondered, because of the instructions and how they were printed or how they were explained to patients, if the patients just didn't do the proper test.

And it's hard to -- I mean every day, as clinicians, we go into our offices and we tell people things and think they've got dead-on what we said, and it went right over their head. So I guess my feeling about that is that we probably put enough into the education process and it's really important how the specimens are collected. Can you address some of that a little more?

MS. STATZ: Sandra Statz, Exact Sciences.

Of the samples that you're referring to, I think it's important to note, first of all, that of the samples, 95% were returned and were usable, and of those, 98% produced a relevant Cologuard result. However, there were a number that were not processable, which is, I believe, what you're referring to. And in that group, there were 92 samples that we couldn't process because they were received after the colonoscopy was conducted, and therefore the stool itself would not have been representative of a pre-colonoscopy colon.

There were also a number of samples which were overweight, where the stool sample itself weighed over the limit that we can accept. We can't control for that and neither can the patient. However, it's important that we don't test those samples because if the sample is too big, then there's insufficient DNA preservative to ensure a proper sample. The remaining

samples in that group were instances where the sample itself had leaked during transport.

So I do think this does speak to the issue you're raising, and does the subject or the patient understand how to do it. We believe they understood that the containers needed to be closed, but in some cases they may not have been closed tightly or there may have been some leakage due to a gasket.

Now, subsequent to the DeeP-C trial, we have revised the patient instructions and, as I noted earlier, conducted human factors testing to show that there's better understanding of those instructions. We also made some very minor design changes to the gasket to decrease the leakage rate.

DR. BUJOLD: All right, thank you.

The second question: It appears that as the biogenetics of cancer -- and colon cancer in particular -- improves, that with more markers you may be able to increase the sensitivity and specificity of this test. Are you in the process of sorting that out? Are there other markers in the pipeline that you're thinking about testing?

DR. LIDGARD: Graham Lidgard, Exact Sciences.

Yes, we continue to work with the Mayo Clinic in evaluating and identifying new markers that may be beneficial, but that's in the early research stages. And we'll continue to look at improvements in the assay

over time, to be able to increase particularly the advanced adenoma detection rate.

DR. BUJOLD: Yes, all right. Thank you.

DR. PRZYGODZKI: I would just note that it's important for us to remember that we're looking at the application at this point. Future studies are not included in this review.

Dr. McShane.

DR. McSHANE: Lisa McShane.

I had a question about whether you had actually obtained the specimens that had been taken out at the colonoscopy. Were you able to get those and bank them, or do they reside in the institutions where the colonoscopies were performed?

And the reason I ask that is, particularly with the false positive ones, it would be interesting if you had a way to go back and do some of the molecular tests directly on the tissue that was taken out at the colonoscopy to see if you can explain where those signals that you picked up were coming from.

MS. STATZ: Yes. Sandra Statz, Exact Sciences -- again.

We did not include, in the informed consent, collection of tissue or retention of tissue, so we cannot conduct those studies.

DR. PRZYGODZKI: Dr. Skates.

DR. SKATES: Steven Skates.

This is a question for the Sponsor, particularly the follow-up study that they're proposing. I would just like to understand what the thought processes were that went into its design, in particular the three-year gap before you do the Cologuard test again. Why three years? Why not five? Why not one? Why not repeat it every year? Or some other variation. It would be helpful to understand the design criteria.

MS. STATZ: We chose three years based on a couple of factors. One was, the point sensitivity of Cologuard was sufficiently better than that of FIT, which is currently recommended for annual testing. However, we don't know what that estimate is. And on the other side, the estimates based on the invasive tests are in the 5- to 10-year range. Therefore, we chose three because we thought it was a reasonable start point relative to that point sensitivity estimate.

DR. PRZYGODZKI: I'd like to ask the Sponsor a question.

The algorithm that you folks used to come up with the number itself, have you collected any data of all of the cases that you've gone through to see if there's a correlation with value itself, overall -- and there may or may not be? And I can understand that and that's perfectly fine, for clarity, that you will say the cutoff is -- I think it's 183 -- and if it's above, that's positive; if it's below, that's great. But is there any additional information that you folks would like to divulge for our own edification?

DR. LIDGARD: It's Graham Lidgard, Exact Sciences.

As we've described, we're really focusing on a positive/negative test and -- I think -- some of the discussion brought up by the FDA, that people will make decisions based on degree of positivity/degree of negativity, which is not in our claim data and isn't something that we've been able to validate in the system.

DR. PRZYGODZKI: So the number is essentially, for clarity for the patient and the physician that is actually interpreting the result, that positive is positive and negative is negative and nothing else --

DR. LIDGARD: Yes.

DR. PRZYGODZKI: -- above and beyond that.

Thank you.

DR. LIPKIN: Lipkin. I have a question for the FDA staff.

In the FDA presentation, you presented a post-approval -- a Phase IV study -- annual FIT, because this is the standard of care. Could the FDA comment on how one might interpret not having a comparator arm of annual FIT, which is the standard of care?

DR. TZOU: Abe Tzou, FDA.

So without the comparator, I suppose one would just see how many were positive at T0 the first time, and of those positives, what happened on colonoscopy. One would see how many were positive at T3 and just see how that turned out. That would just be what would be available. How would one interpret that? It depends on how clear-cut it is, frankly.

Right? And the issue is, it may not be so clear-cut.

So the hypothetical thing I tried to present was that you could have this thing where it looks like it might not be performing as well the second time, and is that good enough or not? That's why having some context to say, well, an alternative commonly accepted option performance has this type of profile, that helps to provide some context.

So that's just the general idea. If, as proposed, the Panel thinks that this is how you would make pretty clear-cut decisions on that, we would certainly be interested in hearing what the Panel's direction is on those lines. But if the Panel thought, well, if it's not so easy to interpret that by itself, and having a way to put more context on it -- and it might be helpful -- then that would be a different way to go.

DR. SKATES: So the options for an alternative follow-up study that, I understand, you're presenting are with three-year testing: T0 and then testing at annual intervals until T3. That's with Cologuard, but not with FIT. And would an alternative be a comparison of the two in a programmatic, annual testing, two-arm study?

DR. TZOU: So, first, there are different ways to go, so I'm not saying it has to be one way or the other.

DR. SKATES: Yes.

DR. TZOU: So it could be that, as the Sponsor has proposed -- they think, based on the point estimate -- a three-year time frame is a

reasonable starting point for Cologuard. So that would be one approach. If you were to say how does that compare to an annual FIT screening approach, then that would be sort of comparing those separate approaches -- sort of. That would be one approach to do that. One could entertain some approach where one tried to mix those somehow and try to interpret that. That might be more complicated because then you sort of have two things going on at the same time.

But it depends on whether you want to really look at each one separately, on its own, to see how a pattern of the positivity rates at every three years is for Cologuard versus every year for FIT, how that compares; and whether that referral pattern to colonoscopy makes sense or looks similar or not. But that's one approach. I don't think the FDA is saying necessarily that it has to be that way. We're looking just to see what the Panel thinks about that.

DR. SKATES: I guess I was trying to understand what the proposal was on Slide 102, which was -- when it says FIT minus, that means without the FIT; but FIT plus means with it?

DR. TZOU: I think this is just saying -- again, this is not saying this has to be this way. This is saying if one were interested to see how the Cologuard proposal compares to if patients were to do annual FIT instead, that would be patients would be tested with FIT at T0. FIT positives would go to colonoscopy; FIT negatives would be tested again in a year. FIT positives at

T1 would go to colonoscopy; FIT negatives would be tested -- this would just be an annual FIT standard recommendation.

DR. SKATES: Okay. So how does Cologuard fit into that?

DR. TZOU: This would be separate from Cologuard. This would be like a two-arm -- if you wanted --

DR. SKATES: Oh, this would be the second arm --

DR. TZOU: This would be a second arm.

DR. SKATES: -- versus Cologuard every year or --

DR. TZOU: Yes.

DR. SKATES: As the Sponsor has proposed. Or --

DR. TZOU: Well, I think it would still be -- if this Panel thought three years was a reasonable starting point, then it would be Cologuard every three years, as proposed by the Panel, as a separate arm.

DR. WECK: Can you go to Slide 98? This is Karen Weck.

My understanding of the current proposed study is that it's this, it's just Cologuard at T0 and then at Year 3. And I guess the question the FDA has for us is, is this a good study or should there also be an arm with annual FIT testing?

I mean, in my opinion, I think that the way this study is proposed to be designed, which is just to look at Time 0 and Time 3 -- and then the primary outcome being measured is, is there a decrease in positivity at Time 3, indicating that your Time 0 screen was effective? Is that a good

summary?

Okay. I mean, it's a small study, and I think that would be fine given the primary objective. I think if you really want to show that Cologuard performs better than annual FIT, then you would want to have that arm. But you may already have shown that in the previous one-time data.

So I think the proposed study is fine, in my opinion. Would it be strengthened by having a second arm where you did annual FIT screening? Maybe. In that case I would also probably recommend annual Cologuard screening, and you might want to have a different outcome. But I think the way this study is designed, in my opinion, is fine.

DR. PRZYGODZKI: Dr. Hicks.

DR. HICKS: My question was similar. My understanding -- point of information -- was that for T1-T2, it's just offices, correct? Right.

MS. STATZ: Yes, that's correct. At T1 and T2, there would be an office visit.

DR. HICKS: And no other test could be ordered unless the physician felt there was something pertinent, too?

MS. STATZ: That's correct.

DR. HICKS: Okay.

DR. PRZYGODZKI: Dr. Gallagher.

DR. GALLAGHER: Okay. This is Colleen Gallagher.

I also agree with Dr. Weck that the proposed study from the

Sponsor is okay, because I think that by adding annual FIT in between, you're still continuing that comparison kind of study where I don't know that that's still needed -- for one. But also I think that it doesn't necessarily mean that you're going to catch everything year to year, because if we go by what we know so far, that these polyps take two to five years before they change over, I think the three-year time period is appropriate.

DR. LIPKIN: Lipkin. Just very quick.

You know, if I were sitting on an IRB board, I think I personally would have a hard time approving a study that if the patients are coming in for an office visit, not to do the standard of care, which is annual FIT. I'm interested to see what happens. Is there an IRB that has approved the follow-up study?

DR. WECK: But do you think that a colonoscopy --

DR. LIPKIN: I asked the Sponsor.

DR. WECK: -- at Year 3 would be considered standard of care enough? Because they're all having a colonoscopy at Year 3. So does that abrogate the need to do annual FIT testing or not?

DR. LIPKIN: Given that the patients are already there and the relatively modest cost -- once again, I understand that you're saying that this satisfies it. But looking, I guess, at the amount of effort versus the benefit, I personally have a hard time.

DR. LEVIN: Bernard Levin.

Maybe I can shed a little bit of light on your important question, Dr. Lipkin.

We know that we've heard about the natural history of the disease and the sensitivity of Cologuard. So in considering the issue of safety and the appropriateness of an intervention at the next two time points after the first initial Cologuard, I'd like to just show you the data which has been presented by Van Roon.

This is recently published from Holland on the findings of advanced neoplasia, colorectal cancer, and advanced adenomas at different screening intervals: a one-year interval, a two-year interval, and a three-year interval. And we drew some comfort from the fact that the three-year interval data were really not much different from the baseline.

DR. SKATES: Dr. Levin, could you explain -- I'm trying to understand what the percentages are. So 3.6% means 3.6% of patients who were positive? Or what's the outcome here? Percent true --

UNIDENTIFIED SPEAKER: True positives.

DR. SKATES: So there were 1,000 patients screened and 36% were positive with the test, and they had colon cancer. Is that what the interpretation of that is?

DR. LEVIN: Had advanced neoplasia, yes.

DR. SKATES: Or advanced neoplasia. And what about -- is there any false positive information from this study? And how does that compare

for the annual versus two-year versus three-year intervals?

DR. LEVIN: I don't have that information.

DR. SKATES: Because I think that would also help address the question of interval.

DR. LEVIN: Thank you.

DR. LIPKIN: So your question was -- I'm sorry. Your question was, why are there no error bars on this study? Is that your question?

DR. SKATES: No. Well, first of all, what exactly were the numbers referring to? The second was those are the true positives. What about the false positive rate? Because that could vary by time interval substantially, and that could affect the judgment as to whether annual or a three-year interval is appropriate for the follow-up study.

DR. PRZYGODZKI: This interchange actually brings up an opportunity for us to move into the Panel discussion by the Panel itself. Does anybody have any objections to moving in that direction at this point?

UNIDENTIFIED SPEAKER: Does that exclude us going back if we have a question?

DR. PRZYGODZKI: Well, we could. But we would like to try to get our ideas sort of settled at this point.

Does anybody have any objections?

(No response.)

DR. PRZYGODZKI: So thoughts -- thoughts of what you've heard

from the deliberations, from what you had in the packets, from what you've learned.

DR. SKATES: I'd just like to say that I've been very concerned about the false positives, the specificity levels, until I heard Dr. Pennello's presentation about the tradeoff between the true positive and the adverse event rate, and the true positive outweighed that. If there's any perception of concern on my part, that solved that issue about the 85% specificity.

Moving on to the follow-up study, the FDA's presentation -- actually from yesterday -- about dependence versus independence for understanding the biology and how repeat screens could be interpreted, I think, would be served far better with an annual study, or at least a repeat more than just at beginning and at end, having some interval tests.

And I share Dr. Lipkin's concern, and also the tradeoff here, which is that there's going to be more information around the marginal cost if they're already coming in for an office visit. And I would see all of that adding up to annual testing, I think, providing a richer and more interpretable data source from which to address Dr. Ransohoff's issue, which was what is the long-term programmatic effect and sensitivity of a screening program for colorectal cancer? And I think we'll be able to answer that better with richer, more finely spaced data.

DR. PRZYGODZKI: Thoughts by others? Please.

MS. DeLUCA: Jo-Ellen DeLuca.

A question for Dr. Skates. I think I would like to know if that's the case. I'm in doctors' offices a lot. How much is that going to add to my cost of going to the doctor? Do I have to now go through my PCP every year for that? Do I go to my Gastro every other year for that? And is that going to be affordable? And what about the time commitment? Time spent with my doctors with multi-health problems is very -- I go in with my questions in hand; there's no wasted moment. What's going to happen to his time? Is he going to have to spend more time? Is there going to be an update on the tests, even if it's just a part of the blood work?

DR. SKATES: Yes.

MS. DeLUCA: I'm trying to help the Panel get the cost and time.

DR. SKATES: Yes, there's definitely -- with more repeated screening, there's more cost on the system, both from a healthcare provider as well as from the patient, in terms of a benefit tradeoff. However, what an annual study will be able to provide is, what is that tradeoff?

MS. DeLUCA: I recognize that.

DR. SKATES: And if the tradeoff is that there's marginal benefit for doing it every year versus every three years, then a test or a study such as an annual study from T0 to T3 would be able to address that.

MS. DeLUCA: I appreciate what you're saying.

DR. SKATES: And so, therefore, the conclusion at the end could very well be that every three years is sufficient, and then that is what would

be recommended.

MS. DeLUCA: I'm just looking at what's going to get fit into that 16-minute time that the hospital allows them, because they're almost all bought out by office practices.

DR. SKATES: Right. So if the marginal benefit is not there for doing it annually and the study shows that, and then the recommendation is once every three years, then presumably once every three years is going to be sufficient to get the benefit. And it's going to divide the amount of time spent by the physician or the healthcare provider and the patient by one-third over those three years because you're only doing it once every three. So I think it depends on what --

MS. DeLUCA: Who pays?

DR. SKATES: Well, I don't know who pays, but I'm assuming the insurance company or ACA ends up paying.

DR. PRZYGODZKI: But I don't think that's really a major issue for us. I mean, the point is, is the study going to be appropriate for what we need?

MS. DeLUCA: For yearly.

DR. PRZYGODZKI: It appears to me that if it is an annual test to begin with -- at least by recommendations, anyway -- that's one, too. This is to gather more data, and that is what is most important. And as Dr. Skates has mentioned, if we do find out that once every three years is adequate,

well, then, so be it.

Please.

DR. McSHANE: Lisa McShane.

So I share Dr. Skates' sentiment for kind of feeling like I'd like to do it every year. I think that would guard against a situation where we end up with a result that we see that -- say there's no difference between the annual regular FIT and the annual other. We won't know if we could have backed off on the one year because if we do the study every year for the Cologuard, then if we find something in any of those annual testings, we're going to go reflexing to colonoscopy. So we won't really get information on what would have had happened had we not looked at all and therefore not had the opportunity to intervene, if waiting the whole three years. So there's definitely a tradeoff.

MS. FURLONG: I think it's also important to follow standard of care and check annually because you're really not taking into account the age at which the patient entered the system. So the risk increases with age, and you would want to take that into consideration, I would guess.

DR. McSHANE: You could stratify on that. But I guess if you did the one every three years and then one every year and you didn't find that the Cologuard was better -- but if, in fact, had you done it every year and it would have been better, that's why it would lean towards what Dr. Skates was suggesting, to probably do the annual.

DR. LIPKIN: Lipkin.

And if the issue is they don't want to deal with their stool, they're already dealing with their stool, right, because of the nature of the Cologuard test.

DR. WECK: So I actually had some questions about the test itself and the analytic performance, unless people want to still discuss the study.

Yes, okay. So I'm convinced by the clinical sensitivity and specificity data. I just wanted to ask a couple questions about the analytic performance of the test, speaking as someone who runs a molecular laboratory. So I assume I might be running this test.

And so it's really a two-part test, to do the molecular analysis plus the FIT analysis, and I think combining those together is what we need to achieve the sensitivity. So that's excellent. But it does sort of change the way a clinical laboratory might run the test. I think two different sections or two different laboratories might be running the two different components.

So the molecular test might be done in a high-complexity molecular laboratory such as mine, whereas the ELISA test might be done in a different laboratory. And so it may be a little complex to pool the results from two different sections and run the algorithm, but we can figure out a way to do that.

I guess one of my questions really is about what happens if the

ELISA test doesn't work. So I understand that the FIT test is an important part of the algorithm. But if for some reason you only had the molecular results, is there anything, some subset analysis that could be done to report part of the results?

And, in particular, one of the big limitations of the study is if there are individuals who have diarrhea or blood in the stool and that invalidates the FIT part of the test, is there any utility at all of just doing the molecular part of the test?

DR. LIDGARD: So Graham Lidgard, Exact Sciences.

There were three questions and one was, where is the test done? The Cologuard system is an integrated system, and the hemoglobin is actually run on the same STAR platform as the molecular. And so the instrumentation is the same and the plate reader for the assay --

DR. WECK: Okay.

DR. LIDGARD: -- feeds its data into the system. So it's one system. It wouldn't be separate in the lab and something that the lab would have to work out for their own strategies. But I think that's something that has been done before.

The second question was splitting the results. If any one component of the assay fails, it's an invalid result, and there's usually sufficient sample to repeat the test. If it was due to operational errors or procedures within the lab, you could repeat the test.

And the last piece is the piece about the symptoms. Again, that would not be an indication for use if there was blood in the stool or diarrhea. Those are symptoms that we would consider not an asymptomatic patient.

DR. WECK: Thank you, that's fair. I think that there will probably be the desire for people in laboratories to just look at the methylation and KRAS results. But I understand that that's not what the test has been designed to do and that's not what the studies have shown. So it would just be invalid and not indicated, if you don't --

DR. LIDGARD: Yes, it would be just invalid. And, again, I think the important thing, to look at the KRAS results, is the test is detecting the presence. It's not telling you which mutation, and it doesn't tell you which lesion it came from.

DR. WECK: Right, yes.

DR. LIDGARD: And I think for a KRAS test that's been used as a clinical device, it really needs to be done on tissue.

DR. WECK: Yes, I agree with that. Yes, we do KRAS testing in my laboratory all the time, and I agree that that test needs to be done on the colon cancer tissue itself, and it's a completely different indication. I was just thinking about could we pool the methylation and KRAS screening results in some way without including FIT? But your answer is fine. I think that it's no.

So in terms of running the samples, you know -- if I read the package insert, it appears that it's ideal to batch 42 samples per run. So are

you planning that this test would only be available to very large reference laboratories? Or have you thought about packaging it in a way that smaller numbers of samples could be run?

DR. LIDGARD: You can run smaller runs on the system, but unfortunately the system consumes all the reagents --

DR. WECK: Yes.

DR. LIDGARD: -- for the run. It assumes that there's a complete run. So it's not very efficient to run it in --

DR. WECK: Right.

DR. LIDGARD: -- smaller batches.

DR. WECK: It's just something to think about, perhaps, in future marketing, if you want it to be more widespread than just in the very largest reference laboratories.

Then, I guess my final question really is regarding -- I think Dr. Lipkin was asking about controls. So my understanding is that there are controls for each of the three subcomponents of the assay, but I think those are all external controls with the exception of measuring the actin.

And I did want to further ask whether there's any internal control for the methylation component. We run a number of methylation molecular assays in my laboratory, and sometimes, in an individual sample, the bisulfate reaction does not work, so we include an internal control that that bisulfate reaction worked in that sample. Is there any such type of

methylation control -- internal control?

DR. LIDGARD: That's a good question. The actual actin target that we use will only be detected if it's converted by the bisulfate.

DR. PRZYGODZKI: Great.

Dr. Gates.

DR. GATES: No, my question was answered in part of the dialogue.

DR. McSHANE: Just two minor things regarding the discussion we were having earlier about when samples aren't fully evaluable. I guess we have to keep in mind here that these samples can be reproduced, that it's not like a tumor sample where you've taken all the tumor out and if you didn't preserve it well, the whole thing is gone and you have nothing. So here you could always go back for repeat testing.

The issue of the internal controls is related to another question I was going to ask. You know, having had some experience shipping tumor samples across the country and finding occasionally that you'll get a sample that's sitting on a loading dock when it's 105° in Phoenix, Arizona -- you know, it goes bad. And so have you examined those kinds of, what I will call, pre-analytical factors in your robustness studies?

DR. LIDGARD: That's a good question, Dr. McShane. We have done robustness studies on shipping and temperature, and we have a recommended shipping procedure, and that we have used the international

shipping standards temperature cycling and extended high temperature/low temperature to actually demonstrate that the stool and the hemoglobin are stable.

DR. SKATES: This is Steven Skates.

I want to get back to the design of the follow-up study. One of the other possibilities that's just cropped up or come to mind is actually having a two-arm study.

And I want to be clear. I wasn't advocating that FIT be part of these studies. What I was advocating was looking at a finely divided time scale of doing it annually rather than doing it just at T0 and then T3.

But maybe what is the more direct answer to that is to do a two-arm study every year for half the patients and T0 and T3 for the other half, and that way you can directly answer the question. And it's all Cologuard. No FIT needed in there because you've already shown, at one time point, Cologuard is superior to FIT. But this will directly answer the question is there improvement on doing Cologuard every year versus doing it just once every three years?

And there are benefits to both of those. As the patient advocate was pointing out, there's limited time. So if you can get the same result every three years, that's great for the patient and for the healthcare provider. But if you need it every year, then such a study design would answer that directly. So I'm just throwing that out for both the Sponsor and

the Panel.

DR. WINAWER: Dr. Winawer, Memorial Sloan Kettering.

That's a very interesting suggestion. And we've had many other suggestions for designs of the study. I don't think this is going to be the only study that will be performed. If Cologuard is approved, then I'm sure the scientific community is going to jump on a whole variety of studies that will, perhaps, be like yours and others that we have.

I think we need to keep the study very simple and we need to take into consideration a couple of other factors, which are patient factors and also -- well, mainly patient factors. And that is, patients don't like to come back every year. It would be important to have programmatic sensitivity over time, but we have learned that the adherence to annual testing, from the guaiac testing and the FIT testing, that patients don't like to come back.

In the Minnesota study -- which is a very rigorous trial, as we all know -- in the annual arm, 46% of the patients came back every year. In the FIT studies, mainly in the Netherlands, anywhere from 40% to 60% of the patients come back every year. And in our own study with Dr. Zauber and myself that we've just completed, comparing FIT to guaiac-based FOBT and colonoscopy, only 40% of patients came back every year for three rounds. So I think if we set up the study like that, it's doomed to failure.

I think the rationale for the three-year point -- and the other

point in time is if we do Cologuard every year. We're not going to do a colonoscopy every year. So that will address a different question. We are addressing the performance at baseline with all patients having a colonoscopy and performance at T3, all patients having a colonoscopy and comparing performance at T3 with T0. If we do Cologuard each year without colonoscopy, that's a whole different set of questions. And, really, I think it may make the study a little more difficult.

The rationale -- before I turn it back to you, Dr. Skates. The rationale for this is the FIT studies and the FIT recommendations every year were really based on the guaiac-based randomized trials every year. The Minnesota trial had an arm every year, the European trials every other year. And the Minnesota trial had an "every other year." By the way, the "every other year" in the Minnesota trial had a better compliance and better adherence than the "every year."

The rationale for this study, the post-approval study, as I see it myself -- as a clinician, I was not involved in the design. But I heard about the design, and my take on it is that with the high sensitivity of Cologuard for colorectal cancer at baseline, 92% -- and in addition to that, the high sensitivity for high-grade dysplasia, which is the bridge to invasive cancer, really -- basically, it's really clearing out the vast majority of colorectal cancers at baseline.

And then the follow-up, I think, will be primarily to look at the

interval cancers, of course, during that three-year period of time. And hopefully, that will be very few. And then, over the three-year period of time, we're really looking at the progression of advanced adenomas. And at T3, the performance in terms of advanced adenomas will be, I think, the most informative as far as I can see, as a clinician.

DR. PRZYGODZKI: I'd like for us to slowly wind down. If you have a question, please, go right ahead. But I would like for us to move so we can take a little quick break and then get to the FDA questions.

DR. MAHOWALD: Yes, this is probably a quick one.

Mary Mahowald.

I appreciated Dr. McShane's mentioning that this is a duplicable resource and so it's not like we need to excise tissue again. On the other hand, this is not a procedure that people love to undergo to provide a specimen.

And then I was interested in the concerns about transport from one climate to another or what duration of transport. And I wonder if, in the packaging and in the instructions given to patients, there is instruction along those lines. You know, don't keep this too long or how you keep it and how you send it and in what conditions you're going to most likely preserve the specimen adequately. Are those instructions there, as well?

MS. STATZ: Sandra Statz, Exact Sciences.

Yes, the instructions include shipping instructions. The

collection kit itself comes with the return shipping box and the return shipping label. And all the information is repeated within the instructions, along with pictures of how to fill it out, how to complete it, and what the time frames are.

DR. MAHOWALD: And temperatures?

MS. STATZ: Well, it is established to be sent at whatever temperature they're at. You know, patients are instructed to return it within a certain amount of time after collection, and how they need to return it is there. There is no condition on temperature.

DR. PRZYGODZKI: Okay. Having this being done, let's take a 15-minute break and come back at 2:10, and we'll proceed with the questions.

(Off the record.)

(On the record.)

DR. PRZYGODZKI: Please take your seats. Okay.

So at this time, let us focus the discussion on the FDA questions. Panel Members, copies of the questions are in your folders. I would ask that each Panel Member identify him or herself each time he or she speaks to facilitate transcription. And let's go.

DR. HUNTER: This is Nina Hunter, FDA.

There are five questions for panel discussion, and some are multi-part. For each question, I will read the question in its entirety, and then we would like each part to be discussed separately.

Could we have the slide up, please?

Question 1: The DeeP-C study met the primary objectives with respect to both required sensitivity and specificity of Cologuard compared to colonoscopy, with 92.3% sensitivity for CRC and 86.6% AN specificity.

With respect to the secondary objectives, Cologuard sensitivity is higher than FIT for both CRC and AA (92.3 vs. 73.8 and 42.4 vs. 23.8, respectively). Although not a secondary objective, Cologuard AN specificity is lower than FIT (86.6 vs. 94.9).

a. Do these conclusions adequately demonstrate effectiveness of Cologuard within the contexts of the proposed intended use and current recommendations for CRC screening?

b. Based on the results of the pivotal clinical study, do the data provided allow for adequate assessment of the benefits and risks of Cologuard?

DR. PRZYGODZKI: Okay, excellent.

So Subsection (a): Do these conclusions adequately demonstrate effectiveness of Cologuard within the contexts of the proposed intended use and current recommendations for colorectal cancer screening?

Dr. Weck, what do you think?

DR. WECK: I would say yes.

(Laughter.)

DR. PRZYGODZKI: And --

DR. WECK: So I think that the sensitivity data that are shown to be superior than FIT for colorectal cancer and for advanced neoplasia do indicate that this would be useful and appropriate as a screening test. And the only caveat I would make would be that although there is an increased sensitivity for advanced adenoma, as well -- because the sensitivity is 42%, clearly that wouldn't be sufficient to recommend not having colonoscopy if one tested negative with this test.

DR. PRZYGODZKI: Thank you.

Others' opinions?

Dr. Skates, please.

DR. SKATES: Okay.

So I think this is a very impressive study with very positive conclusions. One clarification I would like to gather, which is the intended use, and whether -- since this is a one-time-only study, does the intended use have to say something about that? And I'd like to have some input from the FDA on that because this is something that -- the study is designed as a one-time-only screen, and there are follow-up studies where you're going to do a repeat screening, at least proposed. But it would be helpful to clarify that aspect of the intended use.

DR. TZOU: Thank you for the question.

So it's sort of hinted at in Question 4, so if you wanted to explicitly address that in Question 4 or if you wanted to discuss that now, as

part of this discussion, as Dr. Przygodzki thinks is appropriate, but the FDA certainly would be interested in the Panel's feedback on that and would take that into account as far as appropriate intended use moving forward.

DR. PRZYGODZKI: I think we should wait until 4 and nail it, because I think there are a lot of folks that have thoughts on that, and it would probably crystallize a lot faster, if that's okay with you.

DR. TZOU: Excellent.

DR. PRZYGODZKI: Others, please.

DR. HICKS: I was just concerned about -- you know, the original intended use was as an adjunctive screening test and that that be clarified again, exactly how it plays a role. And that just leaves it out there, sort of, in space. So just find a way to utilize it.

DR. TZOU: So the intended use has also gone through discussion between the Sponsor and the Agency over the course of time that the Sponsor suggested. So I can't recall exactly who brought it up when or when it came back.

I think the general issue, general things to consider are whether it makes sense to use it for the one time in patients who have not initially been tested and how much it makes sense for this repeat testing issue that Dr. Skates just brought up, and what wording might be appropriate along those, sort of, both sides as far as where does it stand for patients who have not been previously tested? Where does it stand for patients who have been

previously tested and might consider reusing it?

So the Panel could weigh in on where they think that's appropriate. And if the Panel has alternative wording or language that they think might clarify that more appropriately, the FDA can consider that, as well. I think what the Sponsor presented this morning was, they're saying adjunctive was -- in a sense, that is part of the menu; but it might not be as well established in a programmatic sense as some of the other options currently available.

But if the Panel has alternative wording or language that they would like the Agency and Sponsor to discuss further, we can certainly do that.

DR. PRZYGODZKI: So Dr. Hicks, do you have any proposition?

DR. HICKS: I think later, actually in their intended use, it talks about that it obviously doesn't replace colonoscopy, and as with any screening test, it should be followed by colonoscopy. They have a lot of statements that clear that part up. But it will be a dealer's choice, then, to decide, because they're asking to do it along standard guidelines, and we've seen the standard guideline, you know, that you should get Hemoccult tests every year and possibly flex sig every five and colonoscopy. I just wanted to make sure that the Panel, everybody feels -- especially -- but yeah, people feel that this is clear enough to the physician.

DR. PRZYGODZKI: Dr. Mahowald.

DR. MAHOWALD: Yes, Dr. Mahowald.

I would question that use of the term "adjunctive" also because if you mean adjunctive in connection with a possible colonoscopy, that's one thing. But that's not what it would necessarily be interpreted as if, for example, standard of care right now is the FIT test annually, and I don't see it as adjunctive to the FIT test. So it seems to me the language could be adjusted. If it is intended to be used as I would like to see it used -- instead of the FIT test -- then the word "adjunctive" doesn't seem appropriate.

DR. PRZYGODZKI: So what word would you suggest?

DR. HICKS: Should it be "alternative"?

DR. MAHOWALD: "Alternative," I would definitely consider and prefer.

DR. PRZYGODZKI: Okay.

Please.

DR. NOSTRANT: I guess I have one concern about the word "diagnostic" colonoscopy. Diagnostic colonoscopy is colonoscopy for symptoms. It also is not replacing surveillance colonoscopy for patients with previous polyps, and that will be misinterpreted by primary care physicians, okay. So I think the wording should be slightly different, I think. But I understand --

DR. PRZYGODZKI: So what is your suggestion?

DR. NOSTRANT: Huh?

DR. PRZYGODZKI: What is your suggestion?

DR. NOSTRANT: I would use both words, not replacing either "diagnostic" for symptoms or "surveillance" after polypectomy removal.

DR. PRZYGODZKI: Others?

(No response.)

DR. PRZYGODZKI: Okay, let's go to (b) so we can then step through Question No. 1: Based on the results of the pivotal clinical study, do the data provided allow for adequate assessment of the benefits and risks of Cologuard?

Please.

DR. SKATES: The answer is yes. I thought the analysis by Dr. Pennello essentially addressed that in a quantitative way and the tradeoff was balanced and completely justified.

DR. McSHANE: Yes, I agree. Although we have to, again, go back to the questions we were just discussing, which is that that's cross-sectional. And so my guess is what is likely to happen here is that people who think this new test is attractive is they will simply swap it for FIT and that it will go into autopilot and be done every year. And so I think we better think about that as we consider refining the wording of the label.

DR. PRZYGODZKI: Very good, okay.

Dr. Lipkin.

DR. LIPKIN: Lipkin.

I think the answer is unequivocally yes. I commend, actually, the Sponsors for doing a very fine job, a detailed job, and a really large study that enables us to have a lot of data really to feel comfortable that this is -- that they have done a good job.

With regard to the labeling, it depends sort of a little, I guess, also on FDA policy. But so far as we know, this is a cross-section test, and it's one time use, and then presumably at the end of this study, however precisely it's designed for the Phase IV study, then we'll have information that can be discussed and what is the appropriate screening interval.

DR. PRZYGODZKI: So what I'm hearing is that most people agree that this is a "yes" and "yes" for both (a) and (b) with the proposition of changing a few words, for example, "adjunctive" to "alternative" and the like.

Does that sound rather reasonable?

Agreed.

Dr. Gutierrez, does this answer your question for No. 1?

DR. GUTIERREZ: Yes, I believe this does. Thank you.

DR. PRZYGODZKI: Thank you.

Question No. 2.

DR. HUNTER: Are there patient subgroups, such as age (e.g., ages 75-79, 80-84, 85 and above), gender, and race/ethnicity where considerations for device performance merit additional labeling?

DR. PRZYGODZKI: Okay, open to discussion.

Please.

DR. NOSTRANT: No. And the reason why simply is that the numbers of patients involved is just too small to say that's a difference. And you have to look at that in conjunction with the increase -- you have to look at that in conjunction with the number of people being screened because of that. My argument would be is that the chance of getting them into a screening program markedly overweighs the potential for a false negative examination.

So I think that there should be no restrictions in labeling because, again, that will automatically reduce the chance that that patient will get into a screening program, any screening program. So that's a decision that the patient and the doctor -- must be explained, and I don't think the label is the way it should be explained to the patient.

It's obviously going to be in follow-up afterwards and the patient's own concerns, the emotional aspects about the chance of having colon cancer, those are all things that have to be -- and that only can be done by the patient and the physician. Or I should say healthcare provider because I think that's very important.

DR. PRZYGODZKI: Dr. Gutierrez, you wanted to say something?

DR. GUTIERREZ: I just want to make sure that we're clear here because this is a little bit of a difficult test. When the Agency says label, it doesn't necessarily mean the label that goes to the patient; it is actually the

label as the whole thing gets labeled. So that part of the label that explains the difference may go to the doctor who needs that data to appropriately deal with the patient.

DR. PRZYGODZKI: It's a multifaceted package.

DR. NOSTRANT: Change it completely.

(Laughter.)

DR. NOSTRANT: I think the labeling should, at least, give information as regards to the potential risk, although, again, the number involved is too small to really say that there even is a risk. I don't think it's scientifically sound to say that there is a risk difference.

DR. PRZYGODZKI: Okay.

Dr. Caggana.

DR. CAGGANA: I agree. I think the numbers right now are too small and by enrolling -- the one thing that's studied into was -- have large enough numbers. And then someone had shown the slide where actually you might catch more cancer in that age group, which typically might not be detected otherwise because of the guidelines for 75 and over.

DR. PRZYGODZKI: Thank you.

Dr. Skates.

DR. SKATES: So I was pleased, actually, to see the intended use have an age range cutoff of age $>$ 50 because that's what the study population was, and I think that's what we can extrapolate to.

There was a significant, quite a significant, increase with specificity as age increased. I don't know how that is going to quite affect the label, but what I'd like to see is the risk/benefit analysis that Dr. Pennello did stratified by age and to see if that increased specificity markedly changes that tradeoff.

If it does, then we might want to have some wording, particularly about the decreased specificity, I should say, with age -- so increased false positive rate -- in the labeling about warning the healthcare provider that there could be more false positives as patients get older, particularly if that risk/benefit analysis changes things. If it doesn't, then maybe it's a moot point.

DR. PRZYGODZKI: Please.

DR. BUJOLD: One other thing to add to that, which was alluded to yesterday. You know, you have all these false positives at the age of 65 and over, but also the incidence of problems, complications with colonoscopies is a lot higher in patients, and the prep is a lot more difficult in a lot of those patients 75 and older. And so maybe there should be something added in that regard, too.

DR. MAHOWALD: Mary Mahowald.

I'm a little resistant to not offering more information on the label. I understand you don't want to decrease the number of people who will take the test, but I think, for example, of when I pick up a new

medication, I get this huge insert identifying every little thing that might possibly go wrong -- even a miniscule possibility.

Now, a lot of people don't read all of those long-worded inserts, but they're there, and it just seems to me that there is some obligation to indicate to users that there's a less effective use for a certain group of patients than another, even though it's not terribly statistically compelling.

DR. PRZYGODZKI: Dr. Skates, would you like to say -- okay.

DR. WECK: So I agree, I think, with what's been said before, in particular that the increased false positive rate in older people should be mentioned, since that was significant and went up with age. So there's a very nice stratification, even though the rate was still somewhat small, and that the risk/benefit ratio of doing the test still might be that one would want to do it in older people. So I like the indication for testing, but just including that information of an increased false positive rate in older people and maybe even providing these numbers.

The other thing, you know, in terms of the ethnicity, it was striking that the sensitivity of the test was only 62.5% in African Americans. But the number was so small, with only eight people, that I just don't know whether that should be mentioned or not in the package insert. The most, I think, you would want to say, there may be a decreased sensitivity in African Americans. But without statistically significant numbers, I'm kind of on the

fence about that.

I certainly -- and I'd like to hear Dr. Skates' point of view -- but I certainly think that the information that I saw in there that American Indians and Alaskan natives may have an increased sensitivity of detecting adenomas, that should not be in there. The numbers were way too small, and I would recommend not including that.

DR. SKATES: Steve Skates.

I did look at that African American lower sensitivity. It's based on a denominator of 8. I just think it's too small. The p-value is marginally significant, but multiple comparisons will wipe that out. I think we may need more data to make a positive statement and include that information on the label. So I think the age was very clear. I think the African American should await more data, definitive data.

DR. PRZYGODZKI: So thoughts about noting this as a question for African Americans or not bringing it up in the label itself?

DR. SKATES: I don't think we've got data to bring it up in the label, and so not solid enough data yet.

DR. PRZYGODZKI: And if that's the case, now the other question is also gender.

DR. MAHOWALD: I thought I read there was statistical significance on gender.

DR. SKATES: Yes, there was. But I didn't think the clinical

difference was such that it needed to be mentioned. I don't think it would make a difference whether you're male or female, given the high sensitivities in both cases, that this test would still be recommended. The fact that they're somewhat different statistically I don't think has a clinical implication on it.

DR. MAHOWALD: Would you be open to language regarding age and gender that employed the verb you're using, "may" be some differences?

DR. SKATES: I would be open to it, but it's not something I'd be pushing for. The age, yes; but the gender, I'm not very solid on.

DR. PRZYGODZKI: I'm not sure if it really makes a difference.

DR. McSHANE: Yes, that's what I was going to say. I agree with that statement. I don't think it makes a difference. I mean, if you have it high enough in both groups, why do you care if it's 82% versus close to 100%?

DR. NOSTRANT: Yes, I guess also the specificity issue in the older patients, if I am correct -- and correct me on this -- was that even though the specificity went down, the sensitivity in that group for detecting a real cancer was much greater, and therefore, the percentage of that actually went up 15-fold, if I don't --

DR. WECK: I think it was the positive predictive value, so the sensitivity wasn't equal. But because the prevalence is so much higher, the positive predictive value actually went up, but only, I think, in the very largest

age group.

DR. NOSTRANT: Yes. Again, another reason for us to at least consider that the test should be performed and not to prevent that --

DR. WECK: Agree, absolutely.

DR. PRZYGODZKI: So could I propose that Question No. 2, that there is no great recommendation other than to note potentially that there's an increased false positive rate with increasing age?

DR. WECK: I agree with that. I just have one other point regarding patient subgroups, that -- it's not related to age and gender. But in regards to the labeling indications and contraindications, is the wording "diagnosed with a high-risk for colorectal cancer" as a contraindication explicit enough? Is that typical to just say "high-risk condition" and assume that clinicians will know what that means, or would you want to specifically state "inflammatory bowel disease," you know, "Lynch syndrome," "positive family history of cancer"?

DR. HUNTER: The list is actually much longer than what was presented, so it would have those listed out.

DR. PRZYGODZKI: Okay. So with that, does that satisfy --

DR. HICKS: I just want to, before we leave the subject about the sensitivity changes as they get older with specificity dropping off, this is going to be an interesting -- and won't be for this committee to decide, but clinically, as people are now deciding, payers and government, about are we

going to colonoscope people over 80, this is now coming up.

Is this going to change or are we going to be able -- if we give the test to people, then what are we going to do here? Are we going to scope them or not? Or are we just not going to give the test? That's really an issue for a screening task force to decide.

DR. NOSTRANT: That's an issue for the patient and the physician, not an issue for the FDA.

DR. PRZYGODZKI: Right. I think, actually, that really is a diversion of what we're trying to get at --

DR. HICKS: I'm pointing out we don't make that decision. I'm just telling you this is a forethought that that's going to be one of the effects of this, is a screening task force -- what are you going to do for colonoscopy if you find somebody, 80, and it ends up being positive, what are you going to do? I think that my gastroenterology and other surgical colleagues understand what I'm talking about here.

DR. PRZYGODZKI: Please.

DR. LIPKIN: Lipkin, very quickly.

So I raised the issue before about these different subgroups and colon cancer events, adenoma. We can't do this right now, but it would be interesting to see, sort of, the combined -- sort of all bad things lumped together to see what the statistics look like. So it can't be done today, but the FDA can do that later on and I think relatively quickly.

But there's a comment here that, you know, given -- we talk a lot about statistical issues, but I'm troubled sometimes with this issue of, you know, we can ask 20 safety questions and we have one efficacy question. And there does have to be some sort of discount; you get multiple hypothesis testing here and a false discovery rate.

So I think my own view on this is that, based on the data at hand, we don't really have evidence that these subgroups are real and it should be included on the label. The future of that may change and then we have to take into account, too, we don't want to deny particular groups the benefit, potential benefit at least, of using the screening test.

DR. PRZYGODZKI: Okay.

DR. SKATES: I mean, do you not think the false positive rate with age increase is real or -- and therefore shouldn't be included?

DR. LIPKIN: We discussed the issue of age in particular, once again, with increase in methylation. So at the moment -- it's a gray area, I admit. My own view would be probably to be a little more cautious on it, but one of the nice things about this kind -- this is not a cross-sectional issue in terms of this test presumably going forward; there would be additional data, there will be additional revisions that can be made. But at the moment, my instinct would be not to include that.

DR. PRZYGODZKI: We can also maybe put that, as you move forward and you want to tell the individual his or her risk, it's probably better

to err on some side and at least get some data; how they interpret, how the physician or clinician, whoever, wants to read this and take this into account, that's their purview. But at least we, at least, have that information there. It's not behind the curtain and nobody has an idea what's going on.

So shall we have any additional discussion on this one?

Yes, please.

DR. TZOU: Can I just follow up within a more focused area? So the study design was for 50- to 84-year-olds. How does the Panel view describing the scope as far as upper age range and what is known for performance of the device?

DR. LIPKIN: The patient population was 50 to 84; is that correct?

DR. SKATES: And at the moment, the label says age $>$ 50, so I guess the question is, should there also be an upper age range?

UNIDENTIFIED SPEAKER: A cutoff.

DR. PRZYGODZKI: Yes.

DR. MAHOWALD: Should there be an upper limit?

DR. WECK: I mean, there's no data to indicate there should be because there's no data. So I think greater than age 50 is probably okay, and then include a reference to the study and what was done and what the age was that was tested, because you're going to include the specificity data.

DR. PRZYGODZKI: I personally would say that this is also

intriguing in the sense that they have identified individuals that were above 70 that did have colorectal cancer with this test, which makes one wonder.

DR. SKATES: Well, my view is that we know incidence of a cancer goes up with age; therefore, it's natural to assume that the incidence is just going to keep going up even though we haven't studied it and that the test performance is going to be similar. So my feeling is that there shouldn't be an upper age limit on the intended use.

DR. PRZYGODZKI: So, Dr. Gutierrez, it appears that the only thing that we would like to note is that there may be an increased false positive rate with age and that there is no upper limit other than just basically 50 years and above. Does that answer your question?

DR. GUTIERREZ: Yes, I think that the discussion has been very helpful. Thanks.

DR. PRZYGODZKI: Okay, next question. No. 3.

DR. HUNTER: The DeeP-C study conducted by Exact Sciences was not designed to provide follow-up data on patients that tested negative with Cologuard. What is the appropriate labeling to assure safety and effectiveness for follow-up evaluation of patients testing negative with Cologuard? The FDA would like feedback on follow-up test interval and modality, use of guidelines, and other possible follow-up approaches.

DR. PRZYGODZKI: I suspect this is going to be the interesting part.

How about it, folks? Who wants to go first?

Dr. Lipkin.

DR. LIPKIN: Okay, I'll go first. Lipkin.

So without saying too much, but the time here -- I mean, the answer, at this point, we really don't know. It is a cross-sectional one-time test. What's on the table is a three-year study with three-year follow-up, which certainly seems reasonable in terms of its design. But I personally am still a little troubled by not including FIT in the potential design of a follow-up study, as the FDA suggested, given that patients are already coming in and the minimal cost and effort, balanced against what I think is actually potentially important information that we will get from this minimal increase in effort.

DR. PRZYGODZKI: Would that be a two-arm or just --

DR. LIPKIN: Well, personally, I think it could be done as a one-arm study, but I'll have to think about it.

DR. GALLAGHER: So I think, minus the data that we don't have right now, I think something that says that a negative result does not mean that this person does not need to be followed up in another year per regular standard of care, something like that.

DR. SKATES: I agree. I think that's regular standard of care for a negative test. I thought it was in the label. Yes, that is what's needed.

DR. PRZYGODZKI: Anybody have any objections to the

information as we stated?

(No response.)

DR. PRZYGODZKI: Dr. Gutierrez, does this answer your Question No. 3?

DR. GUTIERREZ: Yes, I think it does.

DR. PRZYGODZKI: Okay, very good.

Question No. 4, please.

DR. HUNTER: Question 4: The proposed device claim does not rule out repeating testing as part of a colorectal cancer screening program. Cross-sectional performance at one time point may not translate to longitudinal performance over time. Data was not provided to support repeat testing with Cologuard.

Cologuard claims do not specify a testing interval. Please discuss whether a longitudinal study should be required to address long-term safety and effectiveness.

DR. PRZYGODZKI: I think to some extent we have discussed this.

Please.

DR. SKATES: So I think it's absolutely required to understand what the programmatic sensitivity, specificity, and other behavior is of a repeat program, repeat screening. The question, then, becomes the design of that additional follow-up study.

And just to clarify, Dr. McShane and I were clarifying previous suggestions, which was there are always -- when you do a clinical trial, if you do a randomized study, that gives you very direct information that couldn't be obtained or could only be obtained indirectly with modeling.

And so as a possibility, that covers both the design that the Sponsors had said and the design that I think people like Dr. Ransohoff were hinting at, and the FDA's presentation about dependence versus independence of testing, having more than just a baseline. And then an endpoint screen would give you that extra data on whether the tests are dependent or independent and therefore how you would structure them, how you would structure the follow-up and interpret repeated negative tests and other variations.

So one randomized design could be T0, T1, T2, and T3: half the patients; and the other half be T0 and T3. And that could all be Cologuard. There wouldn't need to be a FIT component in there as a possibility. You know, I think to some extent that that sort of choice would be up to the Sponsors. But I think that would answer a very scientific question of what is the value of repeat, of frequent repeat, testing.

Does it catch the advanced adenomas that are going to transition or the small adenomas that are going to transition to advanced adenomas before they transition to colorectal cancer, as the FDA presentation pointed out there? There are potentially some natural histories

which are very rapid, and we won't know that unless we do a frequent testing, and we won't know if we can catch them unless we do a frequent testing. And it might be worthwhile to therefore do half the resources on that versus half on T0 and T3.

DR. PRZYGODZKI: Additional comments?

(No response.)

DR. PRZYGODZKI: So it appears that additional testing certainly is warranted with either a one- or two-arm approach and that there would be annual testing either through Cologuard or FIT or some other combination, I guess, at this point.

Does this sound right, from what you folks were saying? Am I hearing this correctly?

DR. McSHANE: I just want to say I really like the proposal of the two-arm randomized with every year versus every three years.

DR. PRZYGODZKI: Great.

DR. McSHANE: I guess I'm a little afraid that if they do just the Time 0 to Time 3, it will be hard to interpret the result.

DR. PRZYGODZKI: Okay. So do we agree on Dr. Skates' --

DR. McSHANE: I don't think you need to include FIT in that.

DR. PRZYGODZKI: Okay.

So do we agree on Dr. Skates' thoughts on the study?

(No response.)

DR. PRZYGODZKI: Dr. Gutierrez, you heard the thoughts on this. Do you -- is the answer --

DR. GUTIERREZ: Yes, I think this is very helpful.

DR. PRZYGODZKI: Okay, very good.

DR. TZOU: Sorry.

DR. PRZYGODZKI: Yes?

DR. TZOU: Could we go back to Dr. Skates' earlier -- about the intended use of whether one time -- or whether there should be wording around one-time use?

DR. SKATES: So I brought up it up as a question because I don't have a clear answer on it. In the intended use, it's not really addressed or perhaps only vaguely, but what I remember is it's not addressed. And I brought it up to see what other people on the Panel thought as to whether it should be explicitly addressed or not. I don't have a clear sense of that answer myself. The study is one time. Just reasoning, it seems rational to think that it works if you're going to repeat it, and so therefore, why not? But you don't have the data to say what the downstream consequences are. So I'd love to hear what everyone else thinks.

DR. WECK: Yes, I agree that -- I don't think the FDA can recommend an interval of testing because there's really no data for that right now, so I think the proposed indications for use are appropriate, as written, for now. There certainly will be additional clinical studies including the

proposed longitudinal study that may help address that and then could be updated. I don't think that the FDA should try to extrapolate and recommend an interval of testing that hasn't been shown yet in a longitudinal study and that isn't currently recommended by clinical groups.

DR. SKATES: So, Dr. Weck, I guess the question in my mind was, should the label say for one time use? That was where I was thinking of, and I'm debating that since the study was only a one-time use study -- and change the label only once we have repeated-use study.

DR. WECK: I see. I don't think so; that's my opinion. Because I think there should be references in there to the study that has been done so far, and that clinicians should be able to use that information along with their patients to decide how to use this test. I think that if you clearly label that it's for one-time use only, that that would restrict it too much.

DR. PRZYGODZKI: Is this adequate?

DR. HICKS: Just a curiosity question about this.

This product, by its presentation today, is indicated that it's more functional and has better sensitivity/specificity than FIT, so we accept that it's a better test. What would it take, what length of study would you say would have to be done -- and maybe you could describe, since you're a statistician -- that would be best to -- maybe it takes FIT's place. Because they're already giving it a national once-a-year okay to use it.

Yes, yearly.

So, today, just the logic is better test; what does it take, statistically, for you to say it could be used?

DR. SKATES: The only concern I have is that there could be some negative downstream consequences with the higher false positive rate on repeat tests, and therefore, you need to limit those repeat false positive tests perhaps by a suitable interval, and we don't know what that interval is. So that's where my concern is.

But I'm very much on both sides of the coin here. I think your point that FIT is already described or prescribed or recommended as an annual test, I think, reassures me and means that you don't need to say only one-time use here. I think that's a reasonable argument.

DR. HICKS: Good.

DR. PRZYGODZKI: Is this adequate, Dr. Gutierrez?

DR. GUTIERREZ: Yes, I think that's helpful.

DR. PRZYGODZKI: Thank you.

So Question No. 5.

DR. HUNTER: Assuming that a longitudinal study is needed to evaluate performance with Cologuard, please comment on the following:

a. Is comparison to a recommended CRC screening option (e.g., annual FIT) needed to evaluate study results and to mitigate study limitations as currently proposed by the sponsor (such as controlling for incident CRC cases, lack of

objective criteria for evaluating study results)?

b. Is the proposed post-approval study adequate to address the following issues?

i. Performance (e.g., number of test negative to positive conversions, diagnostic yield of significant findings, predictive values, adherence to screening and diagnostic follow-up);

ii. Performance across different clinicopathologic characteristics;

iii. Safety concerns (e.g., in the sponsor's proposal, subjects would forgo annual FIT screening during the study duration and repeat Cologuard testing will occur after 3 years).

c. Are there any additional considerations that should be taken into account for the post-approval study?

DR. PRZYGODZKI: It appears that many of the questions have been answered already.

Anybody want to surmise or add to what we've already discussed? That is, at this point, it appears that the proposed study would have to be changed, what the Sponsor has proposed would have to be changed. The study, as Dr. Skates has identified, would probably be a better study.

The question that really comes to mind about the different clinicopathologic characteristics, given that we're looking at colorectal cancer, advanced neoplasia, advanced adenoma, and the different types of adenomas, is there any thought from the Panel on how to push this and get a more cleaner result?

Dr. McShane.

DR. McSHANE: So in other words, are you asking whether there should be specific performance criteria set for the advanced adenomas and a different criteria set for --

DR. PRZYGODZKI: In essence, is it useful or not? Or should we be looking at combining -- looking at just advanced neoplasia aside from colorectal cancer?

DR. McSHANE: Well, I think that's maybe the more important question. I don't think you can set different performance criteria for the two separate ones, for the advanced adenomas and the colorectal cancers, and not the same test. I mean, I think you'd really have to be thinking about altering the tests in some way.

DR. PRZYGODZKI: Sure.

DR. McSHANE: The question about whether you combine or not combine the advanced adenomas with the colorectal cancers, you know, I guess I wouldn't want to give up any sensitivity for detecting the colorectal cancers. So it's not clear to me that if you combine them you're going to get

an answer that you're really happy with for the sensitivity.

So I guess I'm sort of leaning in the direction of saying I would want to design it for criteria for the colorectal cancer endpoint. And I would find out what the advanced adenoma endpoint is, but I might not specifically design the study to hit a particular benchmark in that.

DR. PRZYGODZKI: I would also note, Dr. Skates mentioned that it would be important for us to look at risk analysis stratified by age in this subsection.

Do you still think --

DR. SKATES: Yes. I was encouraging Dr. Pennello -- or requesting Dr. Pennello to stratify his risk/benefit by age just to -- my sense is that the actual change isn't going to be that much that it's going to change the conclusion of the risk/benefit analysis, but I'd like to know that.

DR. McSHANE: Yes. And I would just point out that I think if the relevant parties proceed with the randomized idea, that I think that would help you to get at the advanced adenoma and the colorectal cancer tradeoff because presumably, in every one year, are you going to pick up the advanced adenomas? You'd see how often they progress.

DR. LIPKIN: One thing that -- we're discussing these different categories. I mean, it's clear the test is impressive, really, in what it can do, but the detection rate on advanced adenomas and high-grade dysplasia is not optimal for a screening test and so this merits -- make sure we have follow-

up.

I'm a little concerned about the intervals, some of these developing into full-blown colorectal carcinoma with a detection rate of 42%. In fact, statistically, you can power it, but I don't know how large this study -- one thing I actually -- it's a question for FDA and the Sponsor, what is the size of the proposed follow-up approval study?

DR. PRZYGODZKI: Does the Sponsor --

DR. LIPKIN: Ten patients? Ten patients total? Ten thousand patients? One hundred?

DR. PRZYGODZKI: Does the Sponsor want to respond?

MS. STATZ: Sandra Statz, Exact Sciences.

The proposed patient population is 1,830.

DR. SKATES: And could I understand what that was based on, the sample size? How was that calculated?

MS. STATZ: I'm going to ask Dr. Phil Lavin to describe the sample size calculation.

DR. LAVIN: Phil Lavin, biostatistics consultant to Exact Sciences.

What we did there, in the current PAS that's in your packet, is that we looked at the reduction in the overall proportion who are CRC or AA among the positives. And so statistically that number allows us to see a 40% reduction in that number. So that's basically how it was powered, at 80% power, two-sided 5% Type I error; that's what we looked at.

DR. PRZYGODZKI: Does that satisfy your question?

DR. SKATES: Yes, it tells me how they did it and that's -- I'm sure the calculation is fine. The only question I would have is, is a 40% reduction something that's reasonable, feasible? And that's probably unclear; it's subjective judgment. But gastroenterologists would have to weigh in on that.

DR. PRZYGODZKI: I would assume that probably FDA and the Sponsor would be discussing that at that point.

DR. LIPKIN: Are we done with this point?

DR. PRZYGODZKI: We're looking at all of the subsections in here. I mean, 5a, b.

DR. LIPKIN: Just one tiny thing in (b). Thinking in terms of post-approval study, this would be the first -- at least one -- the first or among the first epigenetic tests that are approved, so I view this as a first-in-class. And I'm a little troubled by this issue that when the test is run, that we're not quite sure about controls for the DNA methylation, which is an important part of the test.

I don't know how technically it would be to incorporate this. It sounds like there are tests that are -- excuse me. There are controls that are run to show that the assay, itself, is working: Is this high, medium, low methylation, I think was the suggestion by -- I think it was Dr. Lidgard.

And I don't know whether the correct control is looking at one

methylation mark or two, or just something like make sure you're within the range of high, medium, and low for the total DNA methylation in the sample. But it just seems, given that we know so relatively much less about the epigenetics than we do about the genetics -- although there's still a lot to know about the genetics, too -- that having some sort of incorporation of this control would be potentially helpful.

DR. PRZYGODZKI: Any additional commentary?

(No response.)

DR. PRZYGODZKI: Does this answer your question, Dr. Gutierrez?

DR. TZOU: Could I again circle back to some of the earlier discussion about demographics, if any of those merited additional postmarket investigation?

DR. WECK: Well, you know, I think one thing that needs to be studied, moving forward, is the sensitivity of the tests in African Americans and the utility of the tests, but I would not require that in the post-approval study. I think the post-approval study should be specifically designed to look at this test in the indicated use in colorectal cancer. You know, I would encourage other people who are designing clinical studies to enroll African Americans to answer that question. But I think because the sensitivity of this test seems to be better than what's currently out there, even in African Americans, that I wouldn't require it as an arm in the post-approval study.

DR. PRZYGODZKI: Is this adequate?

Oh, excuse me.

DR. SKATES: I would just say with 1830, it's going to be hard to weight by various categories. I was thinking of weighting by the older age group, but there's not going to be enough colon cancers, I think, to subdivide it given that the original study was 10,000 to 12,000 and we're having difficulty there in assessing that. I really think that the question should be more frequent versus three years and trying to answer more questions, and that's going to make it more complicated.

DR. PRZYGODZKI: Dr. Gutierrez?

DR. GUTIERREZ: Yes, I think that that's good. Thank you.

DR. PRZYGODZKI: Okay, excellent.

So at this time, the Panel will hear summations, comments, and clarifications from FDA.

You folks have 10 minutes.

DR. HUNTER: We just wanted to thank the Panel Members for your helpful input and thank you for your time in participating here in the panel discussion.

DR. PRZYGODZKI: Excellent, thank you.

And before -- oh, hold on a second.

Before we proceed to the panel vote, I would like to ask the non-voting members, Ms. Furlong -- I'm sorry.

Yeah, there's another section here. Oh, yes.

Do the Sponsors have to say something?

(Laughter.)

DR. PRZYGODZKI: Sponsors, 10 minutes.

I'm looking at this thing, and you can get lost. It's incredible.

MR. CONROY: Believe me, I know everybody wants to end their day. It's been two long days.

DR. PRZYGODZKI: I'm sorry, I will interrupt. I'll say not everybody wants to end the day. We want to have a good review of this, thank you.

MR. CONROY: Kevin Conroy, Exact Sciences.

First, I'd really like to thank the Panel for a tremendously helpful discussion. I know our team got a huge amount out of it, so thank you.

As you've heard over the last couple of days and as you know, colon cancer is a big problem in the U.S. and increasing screening with better tools can help solve that problem hopefully. Approval of Cologuard test, we believe, would provide a new, highly sensitive, non-invasive approach, and we believe it has a place in the current guidelines.

The DeeP-C study was a large study; we did that on purpose. 10,000 patients, 90 sites, broad demographics that matched the population in the U.S. roughly. And that was important for us. What the study showed, we

think, was most important, and that was 92% cancer detection. That is critically important if we're going to go out there, and as Dr. Winawer has said, if you're going to test somebody, you want it to be the highest possibly sensitive test.

Also, the ability of this test to detect pre-cancerous lesions is important; it's a real advancement over the FIT test. And it's really important in the high-grade dysplasia, these precursor lesions that most -- they're the bridge to cancer -- detecting 69%. So these data, we think, really help inform how this test would work in a screening population.

We also want to make sure that the Panel is aware: We understand that there is a false positive rate associated with this test. I think one of the important things that came out was that many of the false positives are a result of the non-advanced adenomas and other polyps. Further study there is important, but I think that's an important finding of the DeeP-C study.

One thing is, is that Exact Science is committed to doing additional research to answer some of these questions that the Panel has put forth. And we commit to working with the FDA to make sure that we do everything that we can to help inform how this test is used per guidelines. We also believe that a lot of other people will be studying this test, hopefully, someday, and that that will inform modeling. And then hopefully there will be long-term government-funded studies that are powerful in nature, like

there had been for these other important cancer screening tests.

The company also commits to working with the FDA on the label language to make sure that it is clear and understandable for patients, for doctors, and for everybody who will come into contact with the test. We think that that is important.

Finally, we'd like to express our appreciation again to the FDA and CMS for this groundbreaking Parallel Review Program, which we think is important, hopefully, for other companies that are innovating new products.

And then, finally, we'd like to thank the Panel for your time and your incredible input. Thank you.

DR. PRZYGODZKI: Thank you, thank you.

I would again like to apologize to the Sponsors, my mishap. I'm just trying to go through the script.

Okay, so now before we proceed to the Panel vote, we'd like to ask the non-voting members to speak.

Ms. Furlong, Consumer Representative, your commentary.

MS. FURLONG: Sure, thank you.

My husband is a family physician and absolutely committed to standard of care. He received a screening colonoscopy, which was negative. FIT tests for the next three years were negative, as well. Five years from the initial screening colonoscopy, he received a diagnosis of Stage IIIC cancer. It came as quite a surprise.

So I feel that the data here was incredibly compelling, and this test shows greater sensitivity than the FIT test. And I feel that this should be part of the arsenal of investigation for and discussion for or diagnosis for colon cancer. So I really do applaud what you've done today and the thoroughness of your exam. And I do worry about that interval of three years because I feel like we might not pick up the cases like my husband's in a timely way.

Thank you.

DR. PRZYGODZKI: Thank you, Ms. Furlong.

Ms. DeLuca, Patient Representative.

MS. DeLUCA: Thank you.

I echo much of what Patricia Furlong said, and I'm a 13-year survivor of rectal cancer. My husband and my father both died of colon cancer, secondary cancer for each of them, but it's something that has affected me, my family. I lead one of the largest support groups in the country with almost 300 members from the U.K., all across the United States, but mostly in rural upstate South Carolina.

This is something that I just hate when I get a call from somebody with their 26-year old son. They don't get tested because a colonoscopy just isn't called for. And I think this would be a wonderful test. I don't think that the FIT kits, as much as their numbers come up, I don't think they're as effective in the patient population. I just think it's the test that

doesn't get done, and I would like to see the test that will get done as being the standard of care.

Thank you.

DR. PRZYGODZKI: Thank you, Ms. DeLuca.

Dr. Gates, Industry Representative.

DR. GATES: Yes, I think this was a well done study with solid data, that's always kind of a thing of beauty, and I think they did a very good job on showing it. I think also the fact that it picks up advanced adenomas at a higher rate is a good thing in terms of being able to pick up precursors sooner, and I think it's a good test.

DR. PRZYGODZKI: Thank you, Dr. Gates.

So now we are ready to vote on the Panel's recommendation to the FDA for Exact Science Cologuard. The Panel is expected to respond to three questions relating to safety, effectiveness, and benefit versus risk.

Ms. Waterhouse will now read three definitions to assist in the voting process along with the proposed indications for use statement for this device.

MS. WATERHOUSE: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert Advisory Panel on designated medical device premarket approval applications that are filed with the Agency. The

PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows:

Safety - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risk.

Effectiveness - There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid Scientific Evidence - Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and

effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

The Sponsor has proposed the following indications for use statement: "Cologuard is intended for use as an adjunctive screening test for the detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of colorectal cancer or pre-malignant colorectal neoplasia. Cologuard is not intended as a replacement for diagnostic colonoscopy. Cologuard is intended to be used in conjunction with colonoscopy and other test methods in accordance with recognized screening guidelines. A positive result in Cologuard, as with any screening test, should be followed by colonoscopy. Cologuard is intended for patients who are typical candidates for colorectal cancer screening: adults of either sex, 50 years or older, who are at average risk for colorectal cancer."

All right, we can now go to the vote.

Panel Members, use the buttons on your microphone to place your vote of yes, no, or abstain for the following questions.

Voting Question 1: Is there reasonable assurance that Cologuard is safe for use in patients who meet the criteria specified in the proposed indications?

(Panel vote.)

MS. WATERHOUSE: Voting Question 2: Is there reasonable assurance that Cologuard is effective for use in patients who meet the criteria specified in the proposed indications?

(Panel vote.)

MS. WATERHOUSE: And Voting Question 3: Do the benefits of Cologuard for use in patients who meet the criteria specified in the proposed indications outweigh the risks for use in patients who meet the criteria specified in the proposed indications?

(Panel vote.)

MS. WATERHOUSE: So for Question 1, all Panel Members voted yes.

For Question 2, all Panel Members voted yes.

And for Question 3, all Panel Members voted yes.

So for Question 1, the Panel voted 10 to 0 the data shows that there is reasonable assurance that Cologuard is safe for use in patients who meet the criteria specified in the proposed indications.

On Question 2, the Panel voted 10 to 0 that there is reasonable assurance that the Cologuard device is effective for patients who meet the criteria specified in the proposed indications.

And for Question 3, the Panel voted 10 to 0 that the benefits of Cologuard outweigh the risks for use in patients who meet the criteria

specified in the proposed indications.

DR. PRZYGODZKI: Well, typically now we normally discuss why Panel Members would say no. That's going to be a different issue. I will open it to the Panel Members for those that want to say some words of their thought, if they would like to express that to the Sponsors.

DR. McSHANE: I would just like to commend the investigators on their study. I thought it was a really well-designed, well-analyzed study. I would make a plea for you to do everything you can to get the specimens this time so that you could do further study.

UNIDENTIFIED SPEAKER: Tissue.

DR. McSHANE: Tissue specimens, yes.

UNIDENTIFIED SPEAKER: From colonoscopy.

DR. McSHANE: Yes, I'm sorry. That's what I meant.

You obviously get the other specimens, but yes. The tissue specimens from the colonoscopy. And blood samples, if you could.

DR. PRZYGODZKI: Please.

DR. BUJOLD: To the Sponsors, I would just like also to commend you on the study, itself. It made the job of this Panel so much easier. It's very difficult when you don't have a properly designed study and you don't have the numbers available. So I would commend you.

DR. SKATES: I would like to also say this is a great study. It's really well designed, a team that spanned a spectrum of all the disciplines

that were needed to execute this. I like the fact that you locked the software down before the study was started. I think that's very important. It gives a great deal of reassurance that there wasn't any tweaking going on after the results came in so that you changed the cutoffs to optimize things.

I think, just having a sense of the past 20 years of being in early detection, this is one of the biggest improvements in early detection that I've seen, and so congratulations to everyone involved, particularly, the statisticians. They often get left out.

(Laughter.)

DR. LIPKIN: I'd like to also commend the Sponsors, echoing what everyone else says. As someone who is not quite there yet in terms of needing colon cancer screening, I'm actually looking forward to having this at least as one of the options that will be available to me.

(Laughter.)

DR. NOSTRANT: Tim Nostrant, University of Michigan.

As a Gastroenterologist, I liked the study as well. I particularly like this because I'm going to get more information and I'm going to get a bigger bang for the buck for the colonoscopies that I do.

Thank you.

DR. PRZYGODZKI: I typically refrain from commentary, but I must say this: I think this is a phenomenal study in particular for one reason. You're actually identifying people with the advanced neoplasia, the large

sessile adenoma. You're looking at the large polyps that you would not otherwise find, and now you have the greater potential to actually cure an individual. I think that's fantastic.

Well, with this, I would like to thank the Panel, FDA, and the Sponsors for their presentations, the time, and the input.

Dr. Gutierrez, do you have any final words?

DR. GUTIERREZ: Yes, if I may. Just a few words.

I don't really want to rain on the parade, but I do want to thank the Sponsor. The Sponsor did something here that is unusual, and I'm going to spend a couple minutes to just describe it because I do think it's important. The Sponsor decided to actually involve both the FDA and CMS, and with the help of the FDA and CMS, they designed a study that really is instrumental in many ways. So the fact that the Sponsor was willing to go the extra step and have a joint review, essentially, from FDA and the CMS is really telling. So I really would like to commend the Sponsor for that.

I would like to thank CMS, who got involved early with us and helped design the studies, helped review the data. I really do think that this cooperation was, at least in this case, really fruitful and we learned a lot, and I believe the CMS also learned a lot of how we do business.

I do want to thank all the Panel Members. We put you through two days of torture. We really do get a lot from the discussions that you have, and all the answers to our questions we really find is invaluable. So I

really do want to thank you all for that.

I'd like to thank the Chairperson. You did a very good job in a difficult two days we put you through.

And I'd like to thank Ms. Waterhouse for all that she has done for all the panel stuff, to put the panel together. That is always a lot of work.

And clearly, last but not least, I'd like to thank the FDA review teams. There's a lot of work that goes in review in this, and both teams, the one today and the one yesterday, they've really done a wonderful job. So I'd like to thank everybody.

DR. PRZYGODZKI: Thank you very much.

And with that, the March 27 meeting of the Molecular and Clinical Genetics Panel is now adjourned.

Thank you.

(Whereupon, at 3:20 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

MOLECULAR AND CLINICAL GENETICS PANEL

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Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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